A functional neuroimaging family study of facial emotion perception in schizophrenia

by

Michael Spilka

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE
DEGREE OF MASTER OF SCIENCE

GRADUATE PROGRAM IN CLINICAL PSYCHOLOGY

CALGARY, ALBERTA

SEPTEMBER, 2014

© Michael Spilka 2014
Abstract

Deficits in facial emotion perception in schizophrenia may be a vulnerability marker for the disorder. Previous neuroimaging studies investigating these deficits were limited by confounding task demands that may recruit other impaired cognitive processes in schizophrenia. We used a family study design along with a passive viewing task to investigate brain activation abnormalities underlying facial emotion perception in schizophrenia and examine whether such abnormalities are associated with the genetic vulnerability for the disorder. Schizophrenia patients, nonpsychotic relatives, and healthy controls passively viewed images of facial emotions during a functional magnetic resonance imaging scan. Region-of-interest and whole-brain analyses revealed hypoactivation in face processing areas for both schizophrenia patients and unaffected relatives compared to controls, and hyperactivation in relatives for frontal regions involved in emotion processing. Our results suggest that activation abnormalities during facial emotion perception represent genetic vulnerability markers for schizophrenia, and may be accompanied by compensatory mechanisms in relatives.

Keywords: facial emotion perception, family study, fMRI, genetic risk, social cognition, vulnerability marker
Acknowledgments

I would like to thank Dr. Vina Goghari for her supervision, as well as the other members of my thesis committee, Dr. Signe Bray and Dr. Giuseppe Iaria, for their input and advice on this project. Acknowledgments go out to Aiden Arnold, Cameron Clark, Irene Liu, Andrea Moir, and Jennifer Prentice for their assistance with various aspects of the project. I also thank the participants who contributed their time to the study, and the members of the CNS Lab for all those times you talked science with me. Many thanks to my family for their enduring support and encouragement. This research was supported by Alberta Innovates Health Solutions, the Canadian Institutes of Health Research, and the Fonds de la recherche du Québec – Santé.
Table of Contents

Abstract...........................................................................................................................................ii

Acknowledgments.............................................................................................................................iii

Table of Contents............................................................................................................................iv

List of Tables......................................................................................................................................v

List of Figures....................................................................................................................................vii

Chapter 1: Introduction.....................................................................................................................1

1.1 Impaired facial emotion perception in schizophrenia.................................................................1

1.2 Impaired facial emotion perception as a vulnerability marker for schizophrenia......................2

1.3 Neurobiology of facial emotion perception..................................................................................4

1.4 Neural basis of facial emotion perception deficits in schizophrenia..........................................5

1.5 Influence of task demands on brain activation............................................................................8

1.6 Current study................................................................................................................................9

Chapter 2: Method............................................................................................................................11

2.1 Participants................................................................................................................................11

2.2. Diagnosis and assessment........................................................................................................11

2.3 Tasks and stimuli.........................................................................................................................12

2.3.1 Passive viewing facial emotion perception task....................................................................12

2.3.2 Functional localizer..............................................................................................................13

2.4 Procedure................................................................................................................................13

2.4.1 Image acquisition..................................................................................................................13

2.5 Data analysis................................................................................................................................14

2.5.1 Functional localizer and ROI analyses..................................................................................15
2.5.2 Facial emotion perception whole-brain analyses………………………………………15

2.5.3 Correlations between neural activation and measures of functioning……………..16

Chapter 3: Results…………………………………………………………………………………………18

3.1 Participant characteristics…………………………………………………………………………18

3.2 ROI analyses: Notable findings…………………………………………………………………18

3.2.1 Facial expressions vs. scrambled faces……………………………………………………19

3.2.1.1 Left FFA…………………………………………………………………………………19

3.2.1.2 Right FFA………………………………………………………………………………19

3.2.1.3 Left and right OFA…………………………………………………………………20

3.2.2 Emotional faces vs. neutral faces……………………………………………………………20

3.2.2.1 Left pSTS………………………………………………………………………………20

3.3 Whole-brain analyses: Notable findings…………………………………………………21

3.3.1 Facial expressions vs. scrambled faces…………………………………………………21

3.3.1.1 Within-group results…………………………………………………………………21

3.3.1.2 Between-group results………………………………………………………………22

3.3.1.2.1 Neutral vs. scrambled……………………………………………………………22

3.3.1.2.2 Sad vs. scrambled………………………………………………………………….22

3.3.1.2.3 Angry vs. scrambled………………………………………………………………22

3.3.2 Emotional faces vs. neutral faces…………………………………………………………23

3.3.2.1 Within-group results…………………………………………………………………23

3.3.2.2 Between-group results………………………………………………………………23

3.3.2.2.1 Fearful vs. neutral…………………………………………………………………23

3.4 Correlations between neural activation and measures of functioning…………………24
Chapter 4: Discussion…………………………………………………………………………………………………………………..26
  4.1 Findings for controls > schizophrenia patients………………………………………………………………………………26
  4.2 Findings for controls > relatives………………………………………………………………………………………………28
  4.3 Findings for relatives > controls and schizophrenia patients…………………………………………………………..29
  4.4 Findings for schizophrenia patients > relatives…………………………………………………………………………31
  4.5 Correlations between neural activation and measures of functioning………………………………………………………32
  4.6 Lack of findings of amygdala abnormalities……………………………………………………………………………………33
  4.7 Complexity of the neural system for facial emotion perception…………………………………………………………35
  4.8 Limitations and strengths…………………………………………………………………………………………………………36
Chapter 5: Tables and Figures…………………………………………………………………………………………………...40
References………………………………………………………………………………………………………………………………54
Appendix A: Examples of Stimuli…………………………………………………………………………………………………..71
Appendix B: Details of the Functional Localizer Task and Region of Interest Analyses……….72
Appendix C: ROI Results for the Supplemental Analyses……………………………………………………………………76
Appendix D: Within-Group Results for the Whole-Brain Analyses…………………………………………………………77
Appendix E: Whole-Brain Activation Results for the Supplemental Analyses…………………81
List of Tables

Table 5.1 Participant demographics.................................................................40
Table 5.2 Antipsychotic medication use in the schizophrenia group..................42
Table 5.3 Frequency of successful functionally-defined regions of interest (ROIs) according to participant group.................................................................43
Table 5.4 Summary of significant ROI analysis results..................................47
Table 5.5 Significant between-group whole-brain activation results.............48
Table 5.6 Pearson correlations of ROI neural activation and measures of functioning........49
List of Figures

Figure 5.1 Average group brain activation z-scores for each region of interest (ROI) and contrast of facial expressions vs. scrambled faces ................................................................. 44

Figure 5.2 Average group brain activation z-scores for each ROI and contrast of emotional faces vs. neutral faces ................................................................. 46

Figure 5.3 Z-statistic map indicating areas of reduced activation in schizophrenia patients compared to healthy controls for the neutral vs. scrambled contrast ........................................ 50

Figure 5.4 Z-statistic map indicating areas of reduced activation in unaffected relatives compared to healthy controls for the neutral vs. scrambled contrast ........................................ 50

Figure 5.5 Z-statistic map indicating areas of reduced activation in schizophrenia patients compared to healthy controls for the sad vs. scrambled contrast .................................................. 51

Figure 5.6 Z-statistic map indicating areas of reduced activation in unaffected relatives compared to healthy controls for the sad vs. scrambled contrast .................................................. 51

Figure 5.7 Z-statistic map indicating areas of greater activation in schizophrenia patients compared to unaffected relatives for the angry vs. scrambled contrast ........................................ 52

Figure 5.8 Z-statistic map indicating areas of greater activation in unaffected relatives compared to healthy controls for the fearful vs. neutral contrast .................................................. 52

Figure 5.9 Z-statistic map indicating areas of greater activation in unaffected relatives compared to schizophrenia patients for the fearful vs. neutral contrast ........................................ 53
Chapter 1: Introduction

Social cognition, which encompasses the cognitive and affective processes underlying social behaviour, has received increased attention in schizophrenia research (Green et al., 2008; Penn, Bentall, Corrigan, Racenstein, & Newman, 1997). An accumulating body of research indicates that impaired social cognition constitutes a hallmark of the disorder, with patients displaying deficits across domains of emotion processing, social perception, theory of mind, and attributional style (Green, Oliver, Crawley, Penn, & Silverstein, 2005; Green & Horan, 2010). Importantly, social cognition has been identified as a significant determinant of real world functional outcome in schizophrenia (Couture, Penn, & Roberts, 2006; Fett et al., 2011).

Furthermore, the association between social cognition and functional outcome appears to be stronger than for neurocognition (another core area of impairment in schizophrenia) (Fett et al., 2011), with several studies suggesting that social cognition mediates the relationship between neurocognition and functional outcome (J. Addington, Saeedi, & Addington, 2006; Brekke, Kay, Lee, & Green, 2005; Sergei, Rassovsky, Nuechterlein, & Green, 2006). The finding of the important association between social cognition and functional outcome in schizophrenia has encouraged efforts to further examine the nature and extent of impaired social cognition in the disorder, as well as the mechanisms involved.

1.1 Impaired facial emotion perception in schizophrenia

An important area of social cognition that is impaired in schizophrenia is facial emotion perception. This ability is a crucial aspect of nonverbal communication, as the face conveys much of the information during social interactions, and this information is necessary for carrying out higher-order social cognitive abilities, such as theory of mind. Although the literature in this area is complicated by considerable variability regarding task type, and demographic and clinical
factors, a meta-analysis of 86 behavioural studies published in the last four decades reported an overall large deficit in facial emotion perception \( (d = -0.91) \) in schizophrenia (Kohler, Walker, Martin, Healey, & Moberg, 2010). Another meta-analysis of 28 behavioural studies utilizing differential deficit designs to examine whether the observed impairments in schizophrenia represent a deficit specific to the perception of facial emotion or whether they are attributable to a generalized deficit in face perception, found that while individuals with schizophrenia are impaired in both facial emotion perception \( (d = -0.85) \) and general face perception \( (d = -0.70) \), a deficit specific to the perception of facial emotions represents a greater impairment (R. C. K. Chan, Li, Cheung, & Gong, 2010).

1.2 Impaired facial emotion perception as a vulnerability marker for schizophrenia

In addition to the above findings confirming the presence of facial emotion perception deficits in chronic schizophrenia, a number of cross-sectional and longitudinal studies have reported impaired facial emotion perception, as well as a significant relationship with functional outcome, in first episode patients and individuals at clinical high risk for schizophrenia (J. Addington, Penn, Woods, Addington, & Perkins, 2008; J. Addington et al., 2006; Amminger et al., 2012; Edwards, Pattison, Jackson, & Wales, 2001; Green et al., 2012; Horan et al., 2012; Kohler et al., 2014; Kucharska-Pietura, David, Masiak, & Phillips, 2005). The presence of facial emotion perception deficits at various phases of the illness, as well as accumulating evidence indicating that such deficits are relatively stable across phases (J. Addington et al., 2006; Green et al., 2012; Horan et al., 2012), suggests that they may represent trait deficits associated with the vulnerability for schizophrenia, rather than state deficits associated with symptomatology.

Given the possibility that impaired facial emotion perception represents a marker of vulnerability for schizophrenia, as well as the robust evidence for the role of genetic factors in
the etiology of psychotic disorders (Cardno & Gottesman, 2000), an increasing number of studies have investigated whether deficits in facial emotion perception exist in unaffected biological relatives, i.e., in individuals who possess an unexpressed genetic/familial risk for schizophrenia. The study of unaffected relatives, referred to as a family study design when both schizophrenia patients and their unaffected relatives are included as well as controls, is a particularly useful approach for studying biological markers of disorder vulnerability and is advantageous for several reasons: 1) studying unaffected relatives, who possess risk genes for schizophrenia, aids to overcome potential confounds associated with the study of psychotic disorders, such as the effects of the disease process, concurrent clinical symptoms and neurocognitive impairment, and side effects of anti-psychotic medication; 2) comparing individuals with schizophrenia to their unaffected relatives can help to isolate neurobiological dysfunction specific to the manifestation of the disorder; 3) including family members who share a genetic risk for the disorder but who do not have the disorder provides the possibility to identify potential compensatory mechanisms that maintain intact cognition and behaviour; 4) vulnerability markers, in comparison to psychiatric diagnoses, are thought to be more closely related to specific neurobiological dysfunction and their corresponding genetic determinants, potentially facilitating the identification of genes involved in the etiology of schizophrenia.

A growing number of studies have investigated facial emotion perception in unaffected relatives. Several studies report reduced performance in relatives compared to controls on emotion recognition tasks for angry faces (Leppänen et al., 2008), neutral faces (Eak et al., 2010), as well as reduced overall impaired performance that is intermediate between healthy controls and schizophrenia patients (Bediou et al., 2007; Erol, Mete, Sonmez, & Unal, 2010; Kee et al., 2004). However, several studies failed to find any performance differences between unaffected
relatives and healthy controls (Bölte & Poustka, 2003; Goghari, MacDonald III, & Sponheim, 2011). Nonetheless, a recent meta-analysis of the growing literature on social cognition abilities in first-degree relatives reported a medium effect size ($d = 0.41$) for facial emotion perception deficits compared to controls (Lavoie et al., 2013). Furthermore, two large-scale multi-family studies of putative neurocognitive vulnerability markers of schizophrenia found that facial emotion perception performance was significantly heritable with moderate-to-strong genetic influence (Greenwood et al., 2007; Gur et al., 2007). Overall, these findings suggest that deficits in facial emotion perception represent a potential marker of genetic vulnerability in schizophrenia, warranting research into the pathophysiological processes involved.

1.3 Neurobiology of facial emotion perception

Findings from basic cognitive neuroscience have identified a complex and distributed system of regions implicated in facial emotion perception in humans. According to the neural model proposed by Haxby, Hoffman, and Gobbini (2000), this system is organized hierarchically and divided into a “core system” for the visual analysis of facial features, and an “extended” system involved in extracting meaning from faces, such as social information. The core system is comprised of several bilateral regions of the visual extrastriate cortex that differentially contribute to face perception: The occipital face area (OFA) is involved in the early perception of facial features, and provides inputs to the other regions making up the core system. The fusiform face area (FFA) responds to invariant features of the face and is therefore thought to represent the perception of face identity. The posterior superior temporal sulcus (pSTS), on the other hand, mediates the perception of changeable aspects of faces involved in social communication, such as eye gaze and mouth shape. While the Haxby et al. (2000) model suggests the functional specificity of regions mediating face identity and expression perception, a recent review of the
literature has challenged the extent to which these two processes are entirely dissociable (Calder & Young, 2005), and the FFA appears to also be sensitive to changes in the emotional content of faces (Surguladze et al., 2003; Vuilleumier & Pourtois, 2007).

While the core system is responsible for the perception of faces, the extended system is composed of brain regions subserving other cognitive functions, which become recruited to process the socially meaningful information contained in faces (Haxby et al., 2000). In the case of facial emotions, several regions involved in processing emotion become part of the extended system. One of the most studied of these regions is the amygdala, which is involved in the automatic evaluation of both salient and ambiguous emotional stimuli, particularly for fearful or potentially threatening stimuli (Breiter et al., 1996; Davis & Whalen, 2001; Isenberg et al., 1999; Phillips et al., 1998). Cortical regions involved in emotion processing and higher order cognition, such as the prefrontal cortex (e.g., orbitofrontal cortex, anterior cingulate, inferior frontal gyrus) and insula, have also been implicated in facial emotion perception (Fusar-Poli et al., 2009).

1.4 Neural basis of facial emotion perception deficits in schizophrenia

In the schizophrenia literature, structural neuroimaging studies have documented abnormalities within the distributed network described above, suggesting that they may play a role in the facial emotion perception deficits observed in the disorder. There is a wealth of evidence for structural brain abnormalities in schizophrenia, including reduced grey and white matter volume (Honea, Crow, Passingham, & Mackay, 2005; Shenton, Dickey, Frumin, & McCarley, 2001), cortical thickness (Kuberberg et al., 2003; Rimol et al., 2010), and white matter connectivity (Kyriakopoulos & Frangou, 2009) in temporal and frontal lobe regions implicated in facial emotion perception. Moreover, abnormalities in these regions have also been found in unaffected relatives, suggesting that these abnormalities in brain structure are associated
with the genetic vulnerability for schizophrenia (Cannon et al., 1998; Goghari et al., 2011; Goghari, Rehm, Carter, & MacDonald, 2007; McIntosh et al., 2006; van Erp et al., 2004); however, others have presented a conflicting view (e.g., Honea et al., 2008).

Abnormalities in brain function associated with impaired facial emotion perception have also been studied using functional magnetic resonance imaging (fMRI). Unfortunately, the literature in this area is rife with methodological heterogeneity and comprised of varied clinical samples, leading to inconsistent results. For example, some studies report under-recruitment of the amygdala in schizophrenia (e.g., Das et al., 2007; Gur et al., 2002), while others have found intact activity (Holt et al., 2005; Seiferth et al., 2009) or hyperactivity (e.g., Holt et al., 2006; Kosaka et al., 2002) during facial emotion processing. Several meta-analyses have attempted to synthesize this body of evidence. H. Li et al. (2010) used an activation likelihood estimation (ALE) approach – a voxel-base technique for examining the distribution of activation foci throughout the brain across different studies – to examine 15 studies of facial emotion processing in schizophrenia. They found that across studies, individuals with schizophrenia had reduced activity in the amygdala, parahippocampal region, fusiform gyrus, right superior frontal gyrus, and right lentiform nucleus, compared to controls. However, several studies included in their meta-analysis used region-of-interest analyses restricted to the amygdala, which may bias the results of a meta-analysis (Taylor et al., 2012).

Taylor and colleagues (2012) attempted to resolve this issue by constraining their ALE meta-analysis to articles that conducted unbiased whole-brain analyses. However, their analysis included studies of emotion perception as well as emotional experience, was not limited to studies using facial stimuli, and focused primarily on contrasts of negative emotions. For studies of emotion perception, it was found that schizophrenia patients underactivated the left
amygdala/hippocampal region and bilateral fusiform gyrus, similar to the H. Li et al. findings. Additionally, they found reductions in right superior temporal gyrus, occipital visual areas, right anterior cingulate, and medial and lateral prefrontal cortices. Unlike the previous meta-analysis by H. Li and colleagues, they also reported regions of greater activation for schizophrenia patients, including the left superior temporal gyrus, cuneus, and parietal lobule, and right precentral gyrus. However, in another recent meta-analysis that focused amygdala activation in response to negative emotional stimuli, Anticevic and colleagues (2012) reported that amygdala under-recruitment by schizophrenia patients was only found for contrasts of negative versus neutral stimuli, and not for studies that directly compared patients and controls on the negative emotion condition.

Overall, while the above findings indicate that facial emotion perception in schizophrenia is linked to functional abnormalities in a diverse set of regions including both visual areas (the “core” system) and areas involved in social-affective processing (the “extended” system), findings remain mixed regarding the extent to which these regions exhibit under-, over-, or similar activation compared to healthy controls.

Very few functional neuroimaging studies of facial emotion perception in schizophrenia have included unaffected relatives, and the results have been conflicting when comparing relatives to controls, including reduced amygdala activation (Barbour et al., 2010; Habel et al., 2004), increased medial temporal, medial prefrontal, and cingulate cortex activation (van Buuren, Vink, Rapcencu, & Kahn, 2011), increased superior frontal and precentral gyrus activation (H. Li et al., 2012), or no difference (Rasetti et al., 2009). A likely contributor to the conflicting findings is the variety of paradigms used, including mood induction, facial emotion ratings, and implicit facial emotion discrimination tasks.
1.5 Influence of task demands on brain activation

In attempting to explain the inconsistent findings in the literature, one explanation is that the majority of previous studies of facial emotion perception in schizophrenia have used a large variety of explicit evaluative tasks (e.g., recognition, labelling, matching, discrimination, intensity rating), which likely recruit a range of cognitive mechanisms that may influence the observed patterns of brain activation. For example, Hariri, Bookheimer, and Mazziotta (1999) demonstrated in healthy participants that while an emotional face matching task led to increased activity in the fusiform gyrus and amygdala compared to a control task, a linguistic labeling task revealed similar fusiform activation but instead also revealed diminished amygdala activation, which was correlated with a simultaneous increase in the right prefrontal cortex. The results suggest that task demands, such as linguistic labeling, may recruit cognitive processes that modulate affective responses during facial emotion perception.

Given the widespread pattern of cognitive impairment in schizophrenia (Reichenberg & Harvey, 2007), and the range of neurocognitive processes recruited by most facial emotion perception tasks (e.g., context processing, set shifting, working memory, attention), the varied activation abnormalities observed in schizophrenia during task performance may in part reflect the influence of these task demands and impaired neurocognitive processes in schizophrenia. Moreover, these task demands may exert a differential effect on schizophrenia patients and healthy controls: In a study by Leitman and colleagues (2011), schizophrenia patients and healthy controls performed a typical facial emotion recognition task in which they were required to identify various facial emotions as being “target” or “non-target”, depending on the specific emotion block being completed. For the statistical analyses, emotion blocks were divided into “threat” (fear and anger) and “affiliative” (happiness and sadness) contexts. It was found that
brain activity in response to an identical non-target emotion stimulus (e.g., fearful face) was influenced by whether it was presented in an affiliative (e.g., happiness block) or threat context (e.g. anger block), indicating the presence of stimulus context effects on the task results. Importantly, the magnitude of the context effects on neural activation was also found to differ between schizophrenia patients and healthy controls, suggesting that group activation differences on similar tasks may result from impaired context processing rather than pure deficits in the perception facial emotions (Leitman et al., 2011).

Similarly, traditional facial emotion recognition tasks may lead to differences in the strategy that patients and controls use to complete the task. For example, Fakra, Salgado-Pineda, Delaveau, Hariri, and Blin (2008) reported that while both patient and control groups similarly displayed the expected pattern of prefrontal-amygdala modulation during a linguistic labelling facial emotion task, this pattern was sustained in schizophrenia patients but not controls during a face matching task, suggesting that schizophrenia patients continued to use a cognitive rather than affective evaluation strategy for both tasks. Overall, the findings from the above studies suggest that task demands associated with traditional tasks of facial emotion perception create potential confounds that limit the ability to study brain activation abnormalities specific to the perception of facial emotion in schizophrenia.

1.6 Current study

In the present study, we attempted to overcome the potential confounds associated with previous tasks by using a passive viewing fMRI task of facial emotion. A passive viewing task that does not require a participant response provides a simple way of studying brain activation underlying facial emotion perception in schizophrenia. Furthermore, we used a family study design to investigate whether activation abnormalities are associated with the genetic
vulnerability for the disorder. Based on the neural model of face perception (Haxby, Hoffman, & Gobbini, 2002), we utilized a region-of-interest (ROI) approach to examine functional abnormalities within key regions of the system for face perception: OFA, FFA, pSTS, and amygdala. It was hypothesized that schizophrenia patients and unaffected relatives would display reduced activation in these regions compared to healthy controls, with relatives displaying activation intermediate between patients and controls. We also conducted whole-brain analyses to examine whether functional abnormalities were present in other emotion processing regions involved in facial emotion perception, such as the prefrontal cortex. Finally, given the important relationship between facial emotion perception deficits and functional outcome in schizophrenia (Horan et al., 2012), we also examined whether brain activation abnormalities underlying facial emotion perception were correlated with measures of social and clinical functioning in schizophrenia patients.
Chapter 2: Method

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 healthy controls. Demographic information is presented in Table 5.1. Schizophrenia patients were recruited through outpatient clinics at the Foothills Medical Centre and community support programs in Calgary, Canada. Research staff identified first-degree biological relatives by completing a pedigree with schizophrenia patients and obtaining permission to contact. Healthy controls were recruited through online advertising and advertisements posted in the Calgary community.

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

2.2 Diagnosis and assessment

Clinical diagnoses were confirmed by the Structured Clinical Interview for DSM-IV Axis I (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997). Interviews were conducted by graduate-
level clinical psychology students or trained research assistants, and diagnoses were made according to DSM-IV-TR criteria during case conferences supervised by a registered clinical psychologist. The Structured Interview for Schizotypy (SIS) (Kendler et al., 1989), with supplemental questions, was administered to assess for Axis II Cluster A personality traits in the biological relatives and healthy controls. The Positive and Negative Syndrome Scale (PANSS) (S. R. Kay, Fiszbein, & Opler, 1987) was used to measure symptom severity in all three groups. The Social Functioning Scale (SFS) (Birchwood, Smith, Cochrane, Wetton, & Copestake, 1990) was used to assess social functioning in schizophrenia patients. Global functioning in all participants was measured by the Global Assessment of Functioning (GAF) Scale (APA, 2000). The two-form version of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was used to estimate IQ for all participants.

2.3 Tasks and stimuli

2.3.1 Passive viewing facial emotion perception task.

The facial emotion perception task in the present study was an adaptation of the Penn Emotion Recognition Test (ER40) (Carter et al., 2009). For the current 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 (see Appendix A for examples of the categories of stimuli). The scrambled faces served as a baseline comparison for the fMRI analyses by providing similar perceptual features as the facial expressions, but without the facial and emotional aspects of interest. Each of the six stimulus categories contained eight different images, for a total of 48 stimuli, which were balanced for the face’s age, gender, and ethnicity. Stimuli were presented one after the other in random order on a black background for a duration of 3000 ms. Each stimuli was preceded by a white fixation cross presented at the
center of the screen, for a jittered inter-stimulus interval with a mean of 4500 ms (range: 3750 – 5500 ms). The total duration for the task was approximately 390 s. The stimuli were presented to participants in the scanner by way of a mounted mirror, and participants were instructed to simply pay attention to the series of images as they appeared.

2.3.2 Functional localizer.

A dynamic functional localizer task (Fox, Iaria, & Barton, 2009) was used to localize brain regions involved in facial emotion perception on a single-subject basis, to be used in the region-of-interest (ROI) analyses. Details of the functional localizer task are provided in Appendix B.

2.4 Procedure

The study was conducted at the Foothills Campus of the University of Calgary, Calgary, Canada. All participants gave written informed consent before participating and participants were debriefed and compensated for their time after completing the study. The study protocol was approved by the University of Calgary Research Ethics Board. Participation in the study occurred over the course of two days. On the first day, participants were assessed with the SCID-I, SIS, PANSS, and SFS. On the second day, participants completed the fMRI functional localizer and passive viewing tasks, and were administered the WASI outside of the scanner.

2.4.1 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 Magnetic Resonance Research Centre, University of Calgary. For each task run, functional T2*-weighted gradient echoplanar images (EPIs) were acquired using the following parameters: slice thickness = 3.4 mm, 40 oblique slices, echo time (TE) = 30 ms, repetition time (TR) = 2500 ms, flip angle = 77°, matrix = 64 × 64, field of view
(FOV) = 22 cm$^2$, with a resulting voxel size = 3.4 × 3.4 × 3.4 mm. One hundred and fifty-six EPIs were acquired for the facial emotion perception task and 159 EPIs were acquired for the functional localizer. Additionally, a whole-brain T1-weighted magnetization-prepared rapid-acquisition gradient echo (MPRAGE) anatomical scan was acquired in order to anatomically register the functional data, with the following parameters: slice thickness = 1 mm, 236 coronal slices, TE = 3.1 ms, TR = 7.4 ms, inversion time (TI) = 650 ms, matrix = 256 × 256, FOV = 25.6 cm$^2$, with a resulting voxel size = 1 × 1 × 1 mm.

2.5 Data analysis

Imaging analyses were performed using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of the FSL Toolbox Version 5.0.6 (FMRIB’s Software Library, www.fmrib.ox.ac.uk/fsl). Non-brain tissue removal was performed using BET (Smith, 2002) and motion correction was performed using MCFLIRT (Jenkinson, Bannister, Brady, & Smith, 2002). In addition, the following pre-statistics processing was applied: slice-timing correction using Fourier-space time-series phase-shifting, spatial smoothing using a Gaussian kernel of 7.0mm at full-width half-maximum (FWHM), grand-mean intensity normalization of the entire 4D dataset by a single multiplicative factor, and highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma = 45.0 s). Functional images were registered to the structural image and then standard MNI (Montreal Neurological Institute) space (MNI152 average template) using 12-parameter affine transformations and a BBR (boundary-based registration) cost function through FLIRT (Jenkinson & Smith, 2001; Jenkinson et al., 2002). Registration from structural to standard space was further refined using FNIRT nonlinear registration (Andersson, Jenkinson, & Smith, 2007a; Andersson, Jenkinson, & Smith, 2007b; Jenkinson et al., 2012). This process was performed separately for each task scan. Estimated
motion time-series plots for the emotion perception task were visually inspected and the mean absolute and relative displacement were analyzed for between-group differences (Table 5.1).

2.5.1 Functional localizer and ROI analyses.

A detailed description of the model fitting for the functional localizer and ROI extraction process, which was carried out in part by Aiden E. Arnold, is described in Appendix B. ROIs included the bilateral OFA, FFA, pSTS, and amygdala. 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 at each ROI for each contrast 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 was violated.

2.5.2 Facial emotion perception whole-brain analyses.

Whole brain analyses were conducted to examine group activation differences in other brain areas. A first-level time-series regression analysis of the facial emotion task was carried out using FILM with local autocorrelation (Woolrich, Ripley, Brady, & Smith, 2001). Six regressors corresponding to each stimulus category were modelled by convolving trial onset times with a canonical (double-gamma) hemodynamic response function, along with their temporal derivatives. Null events (fixation cross) were not modelled and served as an implicit baseline. The six head motion correction parameters were included as regressors of no interest in order to remove motion effects. Additionally, timepoints in the signal that were corrupted by large motion were identified as outliers and included as individual regressors of no interest in order to remove the effects of these timepoints on the analysis. This process was achieved by using FSL Motion Outliers (www.fmrib.ox.ac.uk/fsl) to identify outlier timepoints and generate a confound
matrix corresponding to these timepoints. The confound matrix was then included in the model so that each outlier timepoint was modeled as a separate regressor, resulting in the removal of the effect of these timepoints from the estimation of effects of interest.

For each participant, the following contrasts were computed: 1) each facial expression category (including neutral) was individually contrasted against scrambled faces, 2) each facial emotion category (angry, fearful, happy, sad) was individually contrasted against neutral faces. Additionally, the following exploratory contrasts were computed in order to pool the different stimulus categories together (the results of which are displayed in the Appendices): 3) the weighted average of all facial expressions (including neutral) was contrasted against scrambled faces, 4) the weighted average of facial emotions (angry, fearful, happy, sad) was contrasted against neutral faces. The results of these contrasts were used for the group-level ROI analyses (above) and the whole-brain analyses.

Group averages were obtained by submitting the first-level subject-specific results to a higher-level mixed-effects model analysis in FLAME (FMRIB’s Local Analysis of Mixed Effects) stage 1 (Beckmann, Jenkinson, & Smith, 2003, Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Between-group comparisons of the contrasts defined at the single-subject level were performed using unpaired $t$-tests. Resulting statistics images were thresholded using a cluster-forming threshold of $z > 2.3$ and a cluster significance threshold of $p < .05$, corrected for whole-brain multiple comparisons using Gaussian Random Field (GRF) theory.

2.5.3 Correlations between neural activation and measures of functioning.

In order to explore the relationship between brain activation related to facial emotion perception and measures of functioning in schizophrenia, patients’ SFS mean scaled scores (social functioning), PANSS total scores (symptom severity), and GAF scores (global...
functioning) were correlated with brain activation $z$-statistic values from ROIs and contrasts that revealed significant group differences, using Pearson correlations.
Chapter 3: Results

3.1 Participant characteristics

Participant characteristics are presented in Table 5.1. The three groups did not significantly differ in age Welch’s $F(2, 51.52) = 0.01, p = .99$ (the assumption of homogeneity of variance was violated; therefore, the Welch F-ratio is reported), sex distribution, $\chi^2(2) = 1.57, p = .46$, or handedness distribution, $\chi^2(2) = 2.06, p = .36$. There was a significant group difference in participants’ total years of education completed, $F(2, 79) = 3.51, p = .035$, with schizophrenia patients having fewer years than healthy relatives, $p = .029$. Group did not differ in maternal education, $F(2, 76) = 0.41, p = .665$, or paternal education, $F(2, 69) = 1.23, p = .298$. While groups did not differ significantly on WASI Matrix Reasoning scores, $F(2, 77) = 0.82, p = .443$, there was a significant group difference for Vocabulary scores, $F(2, 77) = 4.79, p = .011$, with relatives scoring higher than both patients, $p = .003$, and controls, $p = .046$. GAF scores differed between groups, Welch’s $F(2, 49.16) = 60.46, p < .001$, with patients having lower scores than both relatives and controls, $p < .001$ for both contrasts. Groups also differed on total PANSS scores, Welch’s $F(2, 49.76) = 33.96, p < .001$, with schizophrenia patients scoring higher than both controls and relatives, $p < 001$ for both contrasts. Healthy relatives and controls had comparable rates of lifetime history of Axis I disorders, $\chi^2(1) = 0.36, p = .55$ All schizophrenia patients were taking antipsychotic medication. Analyses of motion estimates for the facial emotion perception fMRI data indicated that groups differed on the average measure of relative displacement during the scan, Welch’s $F(2, 46.55) = 3.90, p = .027$, with the control group having significantly more displacement than the relatives group, $p = .024$. There were no group differences for mean absolute displacement, Welch’s $F(2, 49.59) = 2.36, p = .11$.

3.2 ROI analyses: Notable findings
The functional localizer task was successfully used to define ROIs for a large proportion of participants for bilateral FFA, OFA, and pSTS; however, the amygdala was only identified for approximately one third of participants (see Table 5.3 for the success rate of the ROI definition for each group). Therefore, analyses were not performed for the amygdala.

3.2.1 Facial expressions vs. scrambled faces.

3.2.1.1 Left FFA.

The brain activation z-scores from contrasts between facial expressions and scrambled faces are presented in Figure 5.1. Significant group differences in activation z-scores were found in the left FFA for several contrasts: A significant group difference was found for the neutral vs. scrambled contrast, Welch’s $F(2, 39.66) = 5.31, p = .009$, such that both schizophrenia patients, $t(42.91) = 2.13, p = .039$, and relatives, $t(33.97) = 3.22, p = .003$, had reduced activation compared to controls. A similar group difference was found for the sad vs. scrambled contrast, Welch’s $F(2, 39.63) = 8.09, p = .001$, with both schizophrenia patients, $t(42.77) = 3.52, p = .001$, and relatives, $t(33.79) = 3.46, p = .001$, having reduced activation compared to controls. In addition, while the omnibus ANOVAs were not significant for the angry vs. scrambled contrast, $F(2, 60) = 2.53, p = .088$, and fearful vs. scrambled contrast, $F(2, 60) = 2.36, p = .103$, planned pairwise comparisons revealed that schizophrenia patients had significantly reduced activation compared to controls for both contrasts, $p = .041$ and $p = .040$, respectively.

The exploratory analysis in which the different facial expressions were averaged together and contrasted with scrambled faces also revealed that patients and relatives had reduced left FFA activation compared to healthy controls (see Appendix C).

3.2.1.2 Right FFA.

Analyses also indicated reduced activation in schizophrenia patients compared to controls
in right FFA: A significant group difference was found for the sad vs. scrambled contrast, $F(2, 68) = 3.65, p = .031$, with pairwise comparisons revealing significantly less activation in patients than controls, $p = .009$. While the omnibus test for the neutral vs. scrambled contrast was not statistically significant, $F(2, 68) = 2.42, p = .097$, the planned comparison between patients and controls was significant, $p = .046$, revealing reduced activation in schizophrenia patients.

A similar pattern was observed for the supplemental analysis in which the weighted average of facial expressions was contrasted with scrambled faces (see Appendix C).

### 3.2.1.3 Left and right OFA.

The sad vs. scrambled contrast revealed significant group differences in other ROIs: For left OFA, $F(2, 60) = 3.27, p = .045$, schizophrenia patients had reduced activation compared to controls, $p = .013$. For right OFA, $F(2, 68) = 3.54, p = .035$, both schizophrenia patients, $p = .013$, and relatives, $p = .047$, displayed reduced activation compared to controls.

### 3.2.2 Emotional faces vs. neutral faces.

#### 3.2.2.1 Left pSTS.

The brain activation $z$-scores from contrasts of emotional faces compared to neutral faces according to ROI and participant group are presented in Figure 5.2. A significant group difference was found for the fear vs. neutral contrast, $F(2, 67) = 5.02, p = .009$, with schizophrenia patients displaying less activation compared to relatives in left pSTS, $p = .002$. This result was driven by schizophrenia patients having less activity (negative $z$-scores) in left pSTS when viewing facial emotions relative to neutral faces.

No significant group differences at any of the ROIs were found for the angry vs. neutral, sad vs. neutral, and happy vs. neutral contrasts. The supplemental analysis in which the emotional faces activation was averaged and contrasted with neutral faces also revealed greater
activation in unaffected relatives compared to schizophrenia patients (see Appendix C).

Due to the large number of neural regions included and contrasts performed, the results reported above were evaluated for statistical significance using an uncorrected alpha level of .05. However, the consistent pattern of reduced FFA activation in schizophrenia patients compared to controls across multiple contrasts suggests that the reported FFA hypoactivation in schizophrenia during facial emotion perception is a robust finding (see Table 5.4 for a summary of the ROI analysis results). In addition, the pattern of results for the majority of the contrasts of facial expressions vs. scrambled faces, despite not reaching significance at each ROI, was in the hypothesized direction of patients and relatives having reduced activation compared to controls (Figure 5.1). In summary, significant group differences were found when contrasting emotional facial expressions with scrambled faces. Consistent with our hypotheses, patients had reduced activation in bilateral FFA and OFA compared to controls for several expressions. As hypothesized, healthy relatives also had reduced activation compared to controls for several expressions; however, this finding was limited to left FFA and right OFA. Contrary to our hypotheses, relatives’ activation was not intermediate between patients and controls, and no group differences in pSTS were found when contrasting expressions vs. scrambled faces. Our hypotheses of group differences were not supported when contrasting emotional faces vs. neutral faces, except for a finding of greater left pSTS activation in relatives compared to patients when viewing fearful emotions.

3.3 Whole-brain analyses: Notable findings

3.3.1 Facial expressions vs. scrambled faces.

3.3.1.1 Within-group results.

Within groups, the contrasts comparing facial expressions to scrambled faces revealed a
distributed pattern of activation underlying the perception of faces, including occipital and
temporal regions forming the core system for face perception, and frontal regions that have been
implicated in the extended system underlying the perception of facial emotions. However, not all
contrasts revealed such extensive activation, and some groups did not display significant
activation for certain contrasts. Within-group results are described in Appendix D.

3.3.1.2 Between-group results.

Group differences were found for several contrasts of facial expressions relative to
scrambled faces (Table 5.5).

3.3.1.2.1 Neutral vs. scrambled.

For the contrast of neutral vs. scrambled faces, both schizophrenia patients (Figure 5.3)
and healthy relatives (Figure 5.4) displayed reduced activation compared to controls in bilateral
FFA and OFA (bilateral in relatives; right only in schizophrenia patients), as well as in the
occipital lobe (lingual gyrus, calcarine cortex, occipital pole).

3.3.1.2.2 Sad vs. scrambled.

A similar pattern was found for the sad vs. scrambled contrast, with schizophrenia
patients (Figure 5.5) and relatives (Figure 5.6) having reduced activation compared to controls in
left FFA and OFA. Schizophrenia patients also displayed hypoactivation in bilateral lingual
gyrus and occipital pole, as well as in left posterior inferior temporal gyrus. Relatives
additionally had hypoactivation in the left cuneus.

3.3.1.2.3 Angry vs. scrambled.

Schizophrenia patients were found to have greater activation than unaffected relatives for
the contrast of angry vs. scrambled faces in paralimbic (bilateral paracingulate, anterior and
posterior cingulate) and frontal regions (bilateral superior frontal gyrus, right middle frontal
gyrus and frontal pole), as well as the bilateral precuneus (Figure 5.7).

No significant activation differences were found for the fearful vs. scrambled and happy vs. scrambled contrasts. Supplemental analyses contrasting the weighted average of facial expressions vs. scrambled faces revealed that controls and schizophrenia patients had different patterns of greater activation compared to relatives. These findings are shown in Appendix E.

3.3.2 Emotional faces vs. neutral faces.

3.3.2.1 Within-group results.

The contrasts between facial emotions and neutral faces revealed a pattern of activation in occipito-temporal and frontal regions involved in facial emotion perception, similar to the one from the comparison of facial expressions to scrambled faces; however, significant activation was only present for the unaffected relatives and schizophrenia patients. These findings are described in Appendix D.

3.3.2.2 Between-group results.

Between-group results from the contrasts of emotional faces relative to neutral faces are presented in Table 5.5.

3.3.2.2.1 Fearful vs. neutral.

For the fearful vs. neutral contrast, relatives displayed greater activation compared to controls in a left frontal lobe cluster that included precentral gyrus, inferior frontal gyrus, and orbitofrontal cortex, and that extended medially through the central opercular cortex and insula to the putamen. This cluster also included the superior portion of the temporal pole (Figure 5.8).

Relatives were also found to have greater left hemisphere activation compared to schizophrenia patients, in inferior frontal gyrus and orbitofrontal cortex, as well as in a temporoparietal cluster comprised of the posterior middle temporal gyrus and pSTS, and extending to the
angular gyrus and posterior supramarginal gyrus (Figure 5.9).

No significant between-group differences were found for the results were found for the angry vs. neutral, happy vs. neutral, and sad vs. neutral contrasts A supplemental analysis contrasting the weighted average of emotional faces vs. neutral faces, however, found a similar pattern of greater left prefrontal activation in relatives compared to schizophrenia patients (Appendix E).

3.4 Correlations between neural activation and measures of functioning

Pearson correlations were performed between schizophrenia participants’ scores on the three measures of functioning (Mean SFS, Total PANSS, and GAF) and neural activation z-scores from ROI contrasts that yielded significant group differences, including the supplemental exploratory analyses (Table 5.6).

Mean SFS score was negatively correlated with ROI neural activation for several contrasts. Specifically, there were significant negative correlations between Mean SFS scores and activation in left FFA for weighted average of facial expressions vs. scrambled faces ($r = - .43, p = .027$), angry vs. scrambled ($r = - .57, p = .003$), and sad vs. scrambled ($r = - .52, p = .006$), such that better social functioning was associated with smaller activation increases when viewing facial expressions relative to scrambled faces. The negative correlation between SFS score and ROI activation for the contrast of sad vs. scrambled faces was also evident in right FFA and right OFA. In addition, activation in left pSTS for the weighted average of emotional faces vs. neutral faces contrast was negatively correlated with SFS score ($r = -.40, p = .044$), and positively correlated with Total PANSS score (higher PANSS scores indicate greater symptom severity) ($r = .43, p = .03$). Given the large number of correlations performed for each measure of functioning, the only significant correlation to survive the Bonferroni-corrected alpha
level of $p < .0042$ was for SFS score and angry vs. scrambled in left FFA.
Chapter 4: Discussion

In the present study, we used a passive viewing fMRI task of facial emotion perception to investigate brain activation abnormalities associated with facial emotion perception in schizophrenia and healthy relatives at genetic risk for schizophrenia. Between-group analyses using functional ROI and whole-brain approaches indicated that both schizophrenia patients and healthy relatives displayed functional abnormalities compared to controls in regions involved in facial emotion perception.

4.1 Findings for controls > schizophrenia patients

Compared to healthy controls, schizophrenia patients displayed reduced activation in bilateral FFA and OFA, as well as areas of the occipital cortex involved in early visual processing. Underactivation of the FFA and OFA, so named because of the sensitivity of these regions to the presentation of faces, has been reported in prior studies of facial emotion perception in schizophrenia (e.g., Seiferth et al., 2009). Consistent with the neural model of face perception (Haxby et al., 2000), the OFA is documented to be involved in the early detection of facial features and provides input to more selective face perception regions, such as the FFA (Fox, Moon, Iaria, & Barton, 2009). The FFA appears to be particularly sensitive to facial identity (i.e., invariant properties of faces) (Hoffman & Haxby, 2000); however, accumulating evidence indicates that it is modulated by changes in facial emotion, suggesting that FFA also contributes to perceiving facial emotion (Fox, Moon, et al., 2009). The visual cortex is involved in the early processing of visual input, and dysfunction at various levels of processing (e.g., perceptual organization, motion processing) has been documented in schizophrenia (Chen, 2011; Silverstein & Keane, 2010). The findings of the present study therefore suggest that impaired facial emotion perception in schizophrenia is due at least in part to an under-recruitment of
regions involved in processing basic perceptual features of faces and the detection of changes in facial expressions, in contrast or in addition to other processes that contribute to facial emotion perception, e.g., dysfunction at the level of associating a perception with emotional knowledge and experience, or impairment in processing contextual information necessary for understanding the perception.

While underactivation of left FFA was found for all the different contrasts between facial expressions and scrambled faces except for happy faces, right FFA and bilateral OFA underactivation was only found for sad and neutral contrasts (although the supplemental ROI analysis for the weighted average of facial expressions vs. scrambled faces also found significant right FFA activation). Although some studies have reported reduced activation in these regions when viewing other emotions (e.g., Habel et al., 2010; Seiferth et al., 2009), group differences are often not consistently observed across all stimulus categories within studies, and many studies combine across stimulus categories, making it hard to interpret the lack of consistency in the current findings. It has been suggested that neutral and sad expressions are more configurally similar to each other than other expressions (Adolphs, 2002); therefore, something about the feature configuration of these expressions may be linked to the similar pattern of neural dysfunction we observed. Hypoactivation was also found in left posterior inferior temporal gyrus when contrasting sad vs. scrambled faces, perhaps suggesting that the sad faces were associated with reduced activation throughout the ventral visual processing stream involved in stimulus identification and recognition (Goodale & Milner, 1992).

Interestingly, previous meta-analyses have suggested that impaired FFA activation in schizophrenia might be restricted to explicit tasks requiring participants to make a judgment about the emotional valence of a face (Li et al., 2010; Taylor et al., 2012). This observation was
not supported by the current results of hypoactive FFA in schizophrenia when passively viewing facial expressions compared to scrambled faces. Furthermore, we did not find any significant differences between patients and controls in pSTS, which was unexpected given that this region is thought to be responsive to dynamic facial features that are important for conveying emotion. However, activation abnormalities in this area have been less consistently reported in the literature than for FFA (Pinkham, 2013).

No differences between schizophrenia patients and controls were found for any of the contrasts between emotional faces and neutral faces. These contrasts are thought to isolate activation specific to processing the emotional aspects of facial expressions, as opposed to the contrast of emotional faces with scrambled faces, which additionally reveals activation underlying general face perception. The lack of activation differences when contrasting facial emotions with neutral faces, and the finding of significant hypoactivation in regions serving basic face perception when contrasting facial emotions with scrambled faces, again suggests that impaired facial emotion perception in schizophrenia occurs at the level of basic face perception. This is consistent with electrophysiological data indicating that schizophrenia patients display reduced event-related potential amplitudes primarily for the N170 component linked to the early structural encoding of facial features, and thought to originate from the fusiform gyrus (Turetsky et al., 2007).

4.2 Findings for controls > relatives

Compared to healthy controls, relatives were found to have similar patterns of hypoactivation in FFA, OFA and early visual areas during the perception of facial emotions. The similar results for both patients and healthy relatives suggest that under-recruitment of these core regions involved in face perception may be associated with the genetic/familial vulnerability for
schizophrenia. Functional abnormalities in these regions have not yet been reported in healthy relatives during facial emotion perception; however, only a handful of fMRI studies of facial emotion perception in schizophrenia have included healthy relatives. However, in an fMRI study of language processing in schizophrenia that included unaffected relatives, X. Li and colleagues (2007) found that both schizophrenia patients and healthy relatives had reduced fusiform gyrus activation during a lexical decision task. In addition, structural MRI studies have found that both schizophrenia patients (Honea et al., 2005) and unaffected relatives (Goghari et al., 2011) have reduced fusiform grey matter volumes, particularly for the left hemisphere. Our finding of left hemisphere hypoactivation in both relatives and patients converges with these findings, and provides additional evidence that occipito-temporal lobe abnormalities in schizophrenia are associated with the genetic vulnerability for the disorder. While the underactivation in healthy relatives was only evident for the neutral vs. scrambled and sad vs. scrambled contrasts, these were also the only contrasts for which whole-brain analyses revealed similar hypoactivation in the schizophrenia group.

4.3 Findings for relatives > controls and schizophrenia patients

Relatives also displayed a pattern of increased left hemisphere activation when perceiving fearful vs. neutral faces, as compared to both controls and schizophrenia patients. Compared to both the control and schizophrenia groups, healthy relatives had hyperactivation in left inferior frontal gyrus and orbitofrontal cortex. Both these regions have previously been demonstrated to respond to the presentation of faces (Ishai, Schmidt, & Boesiger, 2005). The inferior frontal gyrus is thought to be involved in action representation and imitation (Rizzolatti, Fogassi, & Gallese, 2001), and this region has been found to be active both while participants observed or imitated facial expressions (Carr, Iacoboni, Dubeau, Mazziotta, & Lenzi, 2003),
suggesting that action representation may play a role in understanding displays of facial emotion
and other important social cognitive processes such as empathy and theory of mind. In contrast,
the orbitofrontal cortex is known to have strong connections with both limbic and sensory
systems, and is thought to play an important role in emotion processing, including emotion
regulation and the evaluation of social reward (Adolphs, 2002; Kringelbach, 2005). The
observed hyperactivation in these regions may therefore reflect compensatory mechanisms on
the part of healthy relatives, such that processes involved in action representation and emotional
experience were recruited to aid in facial emotion perception. Given that relatives displayed
hypoactivation in core visual areas for face perception that were comparable to the schizophrenia
patients, the compensatory recruitment of prefrontal regions may serve to maintain intact
perception, and help to account for why several behavioural studies report unimpaired facial
emotion recognition in unaffected relatives.

In addition to these regions, relatives also showed hyperactivation in other areas; however, the pattern was different when compared to controls and schizophrenia patients. Compared to controls, relatives also had greater activation in left putamen, insula, central opercular cortex, precentral gyrus, and temporal pole. These regions have been implicated in facial emotion perception and are involved in similar processes as those described above, including somatosensory representation, reward learning, and the representation of self and other’s affective responses (Adolphs, 2002; Kringelbach, 2005; Ochsner, 2008). Therefore, the increased activation in these regions compared to controls may similarly reflect compensatory recruitment of other processes involved in representing emotions.

Compared to schizophrenia patients, relatives had greater activation in left temporo-parietal regions, including posterior middle temporal gyrus, pSTS, angular gyrus and posterior
supramarginal gyrus. Similar to pSTS, the middle temporal gyrus is responsive to emotional faces (Fusar-Poli et al., 2009). The angular and supramarginal gyri are thought to be important for visual attentional processes, such as spatial attention and directing eye gaze (Culham & Kanwisher, 2001). Together, greater activity in these regions likely reflects a greater involvement of perceptual and attentional processes acting in concert with visual regions to process meaningful features of the face (Haxby et al., 2002). Since hyperactivity in these regions in relatives was only found when compared to schizophrenia patients, it is possible that these results are indicative of hypoactivation on the part of schizophrenia patients, rather than compensatory activity in relatives. Additional research is needed to clarify the natures of these findings.

Of note is that the above findings of greater activation in relatives were limited to the contrast of fearful vs. neutral expressions. Previous behavioural studies suggest that performance deficits on facial emotion recognition tasks are more pronounced for the recognition of fear, both for schizophrenia patients (Kohler et al., 2003) and unaffected relatives (Kohler et al., 2014). It is therefore possible fearful expressions were more difficult to perceive, necessitating the recruitment of additional compensatory processes.

4.4 Findings for schizophrenia patients > relatives

When compared to healthy relatives, schizophrenia patients were found to have regions of greater activation for the contrast of angry vs. scrambled faces. A majority of these areas (bilateral anterior cingulate, paracingulate, superior frontal gyrus, posterior cingulate, precuneus) are medial/midline regions that have been associated with the default mode network, which is thought to also play a role in functions that support social cognition, such as perspective taking (Bucker, Andrews-Hannah, & Schacter, 2008; W. Li, Mai, & Liu, 2014). Schizophrenia patients
similarly had greater activation in the right middle frontal gyrus and frontal pole. These regions are part of the dorsolateral prefrontal cortex, which is involved in cognitive control and working memory, and supports goal-directed behaviour (Abe et al., 2007; Braver et al., 1997; MacDonald III, Cohen, Stenger, & Carter, 2000; O’Reilley, 2011). Hyperactivation in these areas might reflect inefficient cognitive processing that may contribute to impaired facial emotion perception in schizophrenia. However, given that we did not find similar hyperactivation when comparing schizophrenia patients to controls, further research is needed to adequately interpret these results.

4.5 Correlations between neural activation and measures of functioning

Our correlational analyses indicated that social functioning was negatively correlated with brain activation z-scores, such that better social functioning was associated with lower activation z-scores (i.e., smaller positive, or greater negative signal change) when contrasting facial expressions with either scrambled or neutral faces. The negative relationship between brain activation and social functioning in surprising, given that the ROIs were selected from contrasts where schizophrenia participants displayed reduced activation compared to controls. However, although the direction of the relationship was negative for most correlations, only the moderate-to-strong correlation between SFS score and left FFA activation for angry vs. scrambled faces survived the Bonferroni-corrected significance threshold. Nonetheless, a number of issues suggest that caution should be exerted in interpreting such strong association between FFA activation and social functioning, including: the large variability in signal change for the contrasts performed, which featured cases with both positive and negative z-scores in all groups; the likely underpowered nature of the study, suggested by the lack of the expected within-group activation of the face processing network for several contrasts; and psychometric issues related to measuring social functioning in schizophrenia (Bellack et al., 2007). Further research is
therefore needed to determine whether this relationship can be replicated.

4.6 Lack of findings of amygdala abnormalities

We did not find evidence of abnormal amygdala activity in the current study. Although several prior studies have reported reduced amygdala activation in schizophrenia during facial emotion perception (e.g., Das et al., 2007), others have found intact activity (e.g., Seiferth et al., 2009). A meta-analysis that focused on amygdala activation reported by fMRI studies of emotion perception found that amygdala hypoactivation in schizophrenia only occurred for contrasts between emotional and neutral faces but not when emotional faces were compared to baseline (Anticevic et al., 2012). However, we did not find group differences in amygdala activation for either type of contrast. Additionally, another meta-analysis by Taylor and colleagues (2012) found that functional abnormalities in amygdala were most consistently reported for implicit rather than explicit tasks. The results of our study, given the passive nature of the task, are not consistent with this finding. However, Taylor et al. included implicit tasks of facial emotion that nonetheless required participants to make evaluative judgments (e.g., identifying face gender). These types of tasks feature cognitive demands that may recruit cortical processes that modulate medial temporal lobe activity, and the extent of this modulation might be different for patients and controls (Meyer-Lindenberg et al., 2005; Phan, Wager, Taylor, & Liberzon, 2002).

Consistent with our results, a recent study that used a true passive viewing task of facial emotion perception also failed to find amygdala hypoactivity in schizophrenia (Mothersill et al., 2014). Taken together, these findings suggest that amygdala dysfunction may not be as relevant to impaired emotion perception in schizophrenia as previously claimed.

There are nonetheless other potential explanations for why we may not have found abnormal amygdala activation in the current study. First, within-group analyses indicated that the
passive viewing of facial emotions did not significantly recruit the amygdala when compared to scrambled or neutral faces (Appendix D), even for fearful faces to which the amygdala is particularly responsive (Breiter et al., 1996). Given that passively viewing photographs and even line drawings of faces has been found to elicit significant amygdala activation when compared to scrambled faces (Ishai et al., 2005), and that the amygdala is implicated in the rapid and automatic detection of emotionally salient stimuli (Murray, Brosch, & Sander, 2014; Sato et al., 2011), it is unlikely that our absence of within-group results can be attributed to factors such as the lack of attentional demands from the passive nature of the task. On the other hand, our supplemental analyses did reveal that healthy controls significantly activated the amygdala when all categories of facial expressions were averaged together and contrasted with scrambled faces (Appendix E). It is therefore likely that the limited number of stimulus trials for each emotion category contributed to a lack of power to detect amygdala activation, which may have precluded the detection of between-group differences within this region.

Many of the studies that reported abnormal amygdala activation in schizophrenia employed ROI approaches, which have the advantage of reducing the severity of correction for multiple comparisons throughout the brain, consequently reducing the threshold for statistical significance. In the current study, the functional localizer ROI approach was unable to define amygdala ROIs for a majority of participants, which prevented us from investigating amygdala activation using this approach. Consequently, the conservative statistical threshold employed in our whole-brain analyses may have been too stringent to detect task-related amygdala activation. The original paper for the functional localizer used in the present study reported comparable success rates for ROI localization of the amygdala (Fox, Iaria et al., 2009), suggesting that the contrast of face and object stimuli does not reliably recruit limbic structures involved in facial
emotion perception. Therefore, the use of alternative strategies, such as anatomically delineated ROIs, may be more appropriate for investigating activation in these structures.

4.7 Complexity of the neural system for facial emotion perception

While our results indicate that dysfunction underlying impaired facial emotion perception occurs at the level of basic face perception, this does not preclude the existence of dysfunction at other stages of processing facial emotions. Importantly, the distributed network serving social cognition is highly interconnected, featuring interactions between regions within this network, as well as multiple processing routes (Adolphs, 2002; Vuilleumier & Pourtois, 2007) For example, the amygdala is known to display an initial early response to emotional faces via a subcortical route, which can have a modulatory effect on the FFA (Vuilleumier, Armony, Driver, & Dolan, 2001; Vuilleumier, Richardson, Armony, Driver, & Dolan, 2004). Similarly, both structural and functional connectivity between face-responsive regions of the occipito-temporal and prefrontal cortex have been demonstrated, suggesting the possibility of reciprocal influence between and within these regions (Adolphs et al., 2002; A. W. Y. Chan, 2013).

In light of the interactive organization of the regions involved in facial emotion perception and social cognition, it is possible that the finding of OFA and FFA hypoactivation in the present study results in part from abnormal connectivity with other regions, such as the amygdala, despite normal regional activation. This hypothesis is particularly relevant given the altered connectivity reported in schizophrenia (Fitzsimmons, Kubicki, & Shenton, 2013). Additionally, the underactivation of OFA and FFA may subsequently disrupt processing at later stages and/or lead to the recruitment of compensatory mechanisms, for example, by submitting an ambiguous perceptual representation from visual areas to frontal cortical regions involved in applying conceptual knowledge to evaluate that representation. Furthermore, the time course of
facial emotion perception is not yet fully understood, with evidence of modulatory effects of emotion occurring at both early and late stages of facial emotion perception (Vuilleumier & Pourtois, 2007). Future studies using task-based functional connectivity approaches, as well as those using approaches with high temporal resolution (e.g., electroencephalography, magnetoencephalography), are needed to 1) further characterize the extent and timing of the interactions between the various processes involved in facial emotion perception, 2) determine where the dysfunction occurs in schizophrenia, and 3) study the effects of compensatory mechanisms on the facial emotion processing network.

4.8 Limitations and strengths

Several limitations of the present study are worth mentioning. As described earlier, groups did not consistently activate the entire facial emotion processing network across all emotion categories, suggesting that our study was likely underpowered. This issue was compounded by the failure of the functional localizer task to identify the amygdala, preventing us from investigating activation in this region using an ROI approach. As a result, our study may have been unable to detect the full range of activation abnormalities during facial emotion perception that are associated with the genetic vulnerability for schizophrenia.

In light of the low power, our most robust finding of FFA underactivation in schizophrenia may stem from the nature of our task contrasts: it has been found that the largest BOLD signal change in the brain in response to viewing faces occurs in the FFA (as opposed to other regions of the system for face perception, such as OFA or pSTS), and this signal change is greatest when contrasting faces with non-face stimuli such as scrambled faces (Kanwisher, McDermott, & Chun, 1997; Kanwisher & Yovel, 2006). Furthermore, the functional localizer used to define the FFA ROI used dynamic stimuli, leading to the possibility that the localizer
was selecting neurons in FFA that respond to changeable features of the face and thus sensitive to changes in facial expression. Therefore, it is possible that abnormal activation in FFA was the easiest to detect from the analyses conducted, without necessarily being the most important locus of impaired facial emotion perception in schizophrenia.

Another limitation concerns the clinical heterogeneity within the patient sample. Our sample of patients included individuals with a diagnosis of schizoaffective disorder or schizophrenia, and we did not differentiate between schizophrenia subtypes. Furthermore, we were unable to control for illness onset, duration, and medication use. While the current study’s sample size prevented us from investigating symptom profiles as a variable of interest, it is possible that the brain activation abnormalities reported are not consistent across illness subtypes. Similarly, the healthy relatives varied in terms of their first-degree relationship to the patients (i.e., relatives were either siblings, parents, or children of patients). While the genetic risk amongst these categories of relatives is roughly equivalent, there is potential variation in terms of psychosocial and environmental (i.e., familial) and risk (MacDonald III, Thermenos, Barch, & Seidman, 2009), which may potentially confound the vulnerability effect on brain activation. Moreover, although attempts were made to match the participant groups on important demographic variables, relatives on average completed more years of education than schizophrenia patients, and also had higher vocabulary scores than the two other groups. Finally, groups differed on the head motion measure of mean relative displacement, with controls having more displacement than relatives. Head motion may modulate the BOLD signal and compromise statistical modeling (Jezzard & Claire, 1999). Although we took several steps to account for motion effects, by including the estimated MCFLIRT motion parameters as nuisance variables in our model and excluding time points that were corrupted by large motion (using FSL Motion
Outliers), it is possible that the group differences in excess motion may have exerted a systematic effect on the BOLD signal, consequently confounding the reported results.

An additional consideration is the passive nature of the fMRI task. Given that the task did not include a participant response, we were unable to control for participant engagement. Although the task was short, it is possible that not all participants were attending to the stimuli for the duration of the task, which would influence neural activity, particularly given the known attentional influences on the face perception network (Vuilleumier et al., 2001). In addition, the lack of a behavioural component meant that we were unable to measure participants’ ability to perceive and recognize facial emotions. Consequently, we cannot directly link the observed activation abnormalities in patients to deficits in facial emotion perception, nor can we with certainty determine whether the patterns of activation in healthy relatives reflect compensatory processes that preserve intact perception, or instead reflect inefficient processing linked to impaired perception. Clarifying this distinction will be an important step in understanding the effect of unexpressed genetic/familial vulnerability on brain function.

Despite these limitations, the current study has a number of strengths. Very few studies of facial emotion perception in schizophrenia have utilized passive viewing tasks free of confounding task demands. This approach is particularly important given the accumulating evidence that task demands from traditional emotion recognition tasks recruit additional cognitive processes that are known to be impaired in schizophrenia. The passive viewing approach is therefore important for clarifying the neural basis of impaired facial emotion perception in schizophrenia. To our knowledge, this is the first fMRI study featuring a purely passive viewing facial emotion perception task that has included unaffected relatives. fMRI family studies are useful for understanding the impact of genetic vulnerability on brain function,
which is vital for uncovering the causes of schizophrenia.

In summary, we found that facial emotion perception in both patients with schizophrenia and their unaffected relatives was associated with hypoactivation in visual regions involved in perceiving the basic features of faces, suggesting that dysfunction of visual processes underlying face perception may be associated with the genetic/familial vulnerability for schizophrenia. Additionally, the hypoactivation in relatives was accompanied by hyperactivation in regions linked to sensory representation and emotional experience, perhaps serving a compensatory role. Discovering potential compensatory mechanisms that maintain intact cognition in relatives may lead to useful targets for remediating impaired facial emotion perception in schizophrenia, and ultimately improving functional outcome for individuals with the disorder.
### Chapter 5: Tables and Figures

#### Table 5.1 Participant demographics

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls</th>
<th>Healthy Relatives</th>
<th>Schizophrenia Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>27</td>
<td>27</td>
<td>28</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.70 (11.10)</td>
<td>41.19 (15.46)</td>
<td>41.07 (11.15)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>13/14</td>
<td>10/17</td>
<td>15/13</td>
</tr>
<tr>
<td>Handedness (R/L)</td>
<td>26/1</td>
<td>22/4</td>
<td>25/3</td>
</tr>
<tr>
<td>Education (years)</td>
<td>15.30 (2.35)</td>
<td>16.20 (2.55)</td>
<td>14.32 (2.96)</td>
</tr>
<tr>
<td>Mother’s Education</td>
<td>13.46 (3.41)</td>
<td>13.07 (3.66)</td>
<td>13.89 (2.99)</td>
</tr>
<tr>
<td>Father’s Education</td>
<td>13.74 (4.68)</td>
<td>12.56 (3.80)</td>
<td>13.50 (3.88)</td>
</tr>
<tr>
<td>GAF</td>
<td>84.67 (5.08)</td>
<td>81.93 (5.39)</td>
<td>53.00 (14.25)</td>
</tr>
<tr>
<td>PANSS Total</td>
<td>33.22 (5.08)</td>
<td>36.56 (5.57)</td>
<td>53.68 (11.98)</td>
</tr>
<tr>
<td>PANSS Negative</td>
<td>7.22 (0.64)</td>
<td>7.74 (1.09)</td>
<td>12.43 (3.94)</td>
</tr>
<tr>
<td>PANSS Positive</td>
<td>7.85 (1.26)</td>
<td>8.70 (1.77)</td>
<td>14.50 (5.27)</td>
</tr>
<tr>
<td>PANSS General</td>
<td>18.15 (3.73)</td>
<td>20.11 (3.54)</td>
<td>26.75 (6.17)</td>
</tr>
<tr>
<td>SFS Mean of Scaled Scores</td>
<td>–</td>
<td>–</td>
<td>113.60 (7.06)</td>
</tr>
<tr>
<td>Matrix Reasoning Scaled Score</td>
<td>12.44 (2.65)</td>
<td>12.59 (1.74)</td>
<td>11.88 (1.82)</td>
</tr>
<tr>
<td>Vocabulary Scaled Score</td>
<td>10.41 (2.68)</td>
<td>11.67 (2.24)</td>
<td>9.77 (1.82)</td>
</tr>
<tr>
<td>Axis I (% with any lifetime non-psychosis diagnosis)</td>
<td>26(^d)</td>
<td>33(^e)</td>
<td>–</td>
</tr>
<tr>
<td>Antipsychotic (Atypical, Typical; % on)</td>
<td>0, 0</td>
<td>0, 0</td>
<td>96, 11</td>
</tr>
<tr>
<td>Antidepressant (% on)</td>
<td>7</td>
<td>7</td>
<td>43</td>
</tr>
<tr>
<td>Antihypertensive (% on)</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Antiparkinsonian (% on)</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Hypnotics (% on)</td>
<td>0</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Other psychoactive (% on)</td>
<td>0</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Patient diagnosis (Schizophrenia: Schizoaffective)</td>
<td>–</td>
<td>–</td>
<td>21:7</td>
</tr>
<tr>
<td></td>
<td>Healthy Controls</td>
<td>Healthy Relatives</td>
<td>Schizophrenia Patients</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Schizophrenia subtypes (Paranoid: Undifferentiated: Residual)</td>
<td>–</td>
<td>–</td>
<td>9:9:3</td>
</tr>
<tr>
<td>Schizoaffective subtypes (Depressive: Bipolar)</td>
<td>–</td>
<td>–</td>
<td>3:4</td>
</tr>
<tr>
<td>Mean absolute displacement from the emotion perception fMRI task (mm)</td>
<td>0.42</td>
<td>0.30</td>
<td>0.29</td>
</tr>
<tr>
<td>Mean relative displacement from the emotion perception fMRI task (mm)</td>
<td>0.13</td>
<td>0.07(^b)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Note.* Mean and standard deviation presented where appropriate. GAF = Global Assessment of Functioning; PANSS = Positive and Negative Syndrome Scale; SFS = Social Functioning Scale.

\(^a\)Less than relatives. \(^b\)Less than controls. \(^c\)Less than patients.

\(^d\)Controls had a lifetime history of the following Axis I disorders (some controls had more than one disorder): alcohol abuse (3 participants), alcohol dependence (1 participant); cocaine dependence (1 participant), major depressive episode (2 participants), hallucinogen abuse (1 participant), major depressive disorder (1 participant), marijuana dependence (1 participant), social phobia (1 participant).

\(^c\)Relatives had a lifetime history of the following Axis I disorders (some relatives had more than one disorder): alcohol abuse (4 participants), alcohol dependence (1 participant), cannabis abuse (1 participant), dysthymia (1 participant), generalized anxiety disorder (1 participant), major depressive episode (1 participant), major depressive disorder (5), panic disorder without agoraphobia (1 participant), posttraumatic stress disorder (2 participants).
Table 5.2 Antipsychotic medication use in the schizophrenia group

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Frequency (% of total patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typical</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>2 (7%)</td>
</tr>
<tr>
<td><strong>Atypical</strong></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>5 (18%)</td>
</tr>
<tr>
<td>Risperidone</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6 (21%)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>
Table 5.3 Frequency of successful functionally-defined regions of interest (ROIs) according to participant group

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Group</th>
<th>Number of Participants (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right Amygdala</td>
<td>Healthy Controls</td>
<td>8 (29.63%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>9 (33.33%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>13 (46.43%)</td>
</tr>
<tr>
<td>Left Amygdala</td>
<td>Healthy Controls</td>
<td>6 (22.22%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>8 (29.63%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>9 (32.14%)</td>
</tr>
<tr>
<td>Right FFA</td>
<td>Healthy Controls</td>
<td>20 (74.07%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>25 (92.59%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>26 (92.86%)</td>
</tr>
<tr>
<td>Left FFA</td>
<td>Healthy Controls</td>
<td>19 (70.37%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>18 (66.67%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>26 (92.86%)</td>
</tr>
<tr>
<td>Right OFA</td>
<td>Healthy Controls</td>
<td>21 (77.78%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>23 (85.19%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>27 (96.43%)</td>
</tr>
<tr>
<td>Left OFA</td>
<td>Healthy Controls</td>
<td>22 (81.48%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>15 (55.56%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>26 (92.86%)</td>
</tr>
<tr>
<td>Right pSTS</td>
<td>Healthy Controls</td>
<td>24 (88.89%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>25 (92.59%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>28 (100%)</td>
</tr>
<tr>
<td>Left pSTS</td>
<td>Healthy Controls</td>
<td>24 (88.89%)</td>
</tr>
<tr>
<td></td>
<td>Healthy Relatives</td>
<td>20 (74.07%)</td>
</tr>
<tr>
<td></td>
<td>Schizophrenia Patients</td>
<td>26 (92.86%)</td>
</tr>
</tbody>
</table>

*Note.* FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus.
Figure 5.1 Average group brain activation z-scores for each region of interest (ROI) and contrast of facial expressions vs. scrambled faces.

Note. SCZ = schizophrenia patients; REL = healthy relatives; CTL = healthy controls. R = right;
L = left; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus.

\( ^* p < .05 \), \( ^{**} p < .01 \), \( ^{***} p < .005 \).
Figure 5.2 Average group brain activation z-scores for each ROI and contrast of emotional faces vs. neutral faces.

Note. SCZ = schizophrenia patients; REL = healthy relatives; CTL = healthy controls. R = right; L = left; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus.

*p < .05. **p < .01. ***p < .005.
Table 5.4 Summary of significant ROI analysis results

<table>
<thead>
<tr>
<th>Contrast</th>
<th>ROI(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Controls &gt; Schizophrenia Patients and Relatives</strong></td>
<td></td>
</tr>
<tr>
<td>Weighted average of facial expressions vs. Scrambled</td>
<td>Left FFA</td>
</tr>
<tr>
<td>Neutral vs. Scrambled</td>
<td>Left FFA</td>
</tr>
<tr>
<td>Sad vs. Scrambled</td>
<td>Left FFA, Right OFA</td>
</tr>
<tr>
<td><strong>Controls &gt; Schizophrenia Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Weighted average of facial expressions vs. Scrambled</td>
<td>Right FFA</td>
</tr>
<tr>
<td>Angry vs. Scrambled</td>
<td>Left FFA</td>
</tr>
<tr>
<td>Fearful vs. Scrambled</td>
<td>Left FFA</td>
</tr>
<tr>
<td>Neutral vs. Scrambled</td>
<td>Right FFA</td>
</tr>
<tr>
<td>Sad vs. Scrambled</td>
<td>Right FFA, Left OFA</td>
</tr>
<tr>
<td><strong>Relatives &gt; Schizophrenia Patients</strong></td>
<td></td>
</tr>
<tr>
<td>Weighted average of emotional faces vs. Neutral</td>
<td>Left pSTS</td>
</tr>
<tr>
<td>Fearful vs. Neutral</td>
<td>Left pSTS</td>
</tr>
</tbody>
</table>

*Note. FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus.*
Table 5.5 Significant between-group whole-brain activation results

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Regions Within Each Cluster</th>
<th>Voxels</th>
<th>Max z-Statistic</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angry vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCZ&gt;REL</td>
<td>R/L paracingulate; R/L anterior cingulate; R/L superior frontal gyrus; R middle frontal gyrus, R frontal pole R/L precuneus; R/L posterior cingulate</td>
<td>1458</td>
<td>3.55</td>
<td>2</td>
<td>36</td>
<td>32</td>
</tr>
<tr>
<td>Fearful vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Happy vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutral vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTL&gt;SCZ</td>
<td>R/L lingual gyrus; R/L FFA; L calcarine cortex; R occipital pole; R OFA</td>
<td>1097</td>
<td>3.37</td>
<td>-18</td>
<td>-82</td>
<td>0</td>
</tr>
<tr>
<td>CTL&gt;REL</td>
<td>R/L FFA; R/L OFA; R/L occipital pole; R/L calcarine cortex, R/L lingual gyrus</td>
<td>7294</td>
<td>3.81</td>
<td>30</td>
<td>-50</td>
<td>-20</td>
</tr>
<tr>
<td>Sad vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTL&gt;SCZ</td>
<td>L posterior inferior temporal gyrus; L FFA; L OFA; R/L lingual gyrus; R/L occipital pole</td>
<td>4570</td>
<td>3.92</td>
<td>-48</td>
<td>-40</td>
<td>-14</td>
</tr>
<tr>
<td>CTL&gt;REL</td>
<td>L OFA; L FFA; L cuneus</td>
<td>2520</td>
<td>3.85</td>
<td>-36</td>
<td>-78</td>
<td>-2</td>
</tr>
<tr>
<td>Angry vs. Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fearful vs. Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REL&gt;CTL</td>
<td>L inferior frontal gyrus; L precentral gyrus; L orbitofrontal cortex; L insula; L central opercular cortex; L temporal pole</td>
<td>1412</td>
<td>3.74</td>
<td>-54</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>REL&gt;SCZ</td>
<td>L inferior frontal gyrus; L orbitofrontal cortex</td>
<td>1371</td>
<td>3.83</td>
<td>-52</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>L posterior middle temporal gyrus; L pSTS; L angular gyrus; L posterior supramarginal gyrus</td>
<td>1292</td>
<td>3.97</td>
<td>-66</td>
<td>-30</td>
<td>-4</td>
</tr>
<tr>
<td>Happy vs. Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sad vs. Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. SCZ = schizophrenia patients; REL = healthy relatives; CTL = healthy controls. R = right; L = left; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus. Region labels were obtained through visual inspection and from the Harvard-Oxford probabilistic structural atlases. Voxels are the number of activated voxels per cluster. x, y, z are MNI coordinates for the peak of each cluster.
Table 5.6 Pearson correlations of ROI neural activation and measures of functioning

<table>
<thead>
<tr>
<th>Contrast and ROI</th>
<th>Mean of SFS Scaled Scores</th>
<th>GAF</th>
<th>Total PANSS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressions vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left FFA</td>
<td>–.43*</td>
<td>–.20</td>
<td>.13</td>
</tr>
<tr>
<td>Right FFA</td>
<td>–.13</td>
<td>–.09</td>
<td>.01</td>
</tr>
<tr>
<td>Angry vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left FFA</td>
<td>–.57**†</td>
<td>–.32</td>
<td>.26</td>
</tr>
<tr>
<td>Fearful vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left FFA</td>
<td>–.35</td>
<td>–.14</td>
<td>.09</td>
</tr>
<tr>
<td>Neutral vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left FFA</td>
<td>–.24</td>
<td>–.05</td>
<td>–.07</td>
</tr>
<tr>
<td>Right FFA</td>
<td>.06</td>
<td>.08</td>
<td>–.14</td>
</tr>
<tr>
<td>Sad vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left FFA</td>
<td>–.52**</td>
<td>–.20</td>
<td>.26</td>
</tr>
<tr>
<td>Left OFA</td>
<td>–.30</td>
<td>–.22</td>
<td>.16</td>
</tr>
<tr>
<td>Right FFA</td>
<td>–.42*</td>
<td>–.13</td>
<td>.27</td>
</tr>
<tr>
<td>Right OFA</td>
<td>–.39*</td>
<td>–.18</td>
<td>.24</td>
</tr>
<tr>
<td>Emotions vs. Neutral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left pSTS</td>
<td>–.40*</td>
<td>–.23</td>
<td>.43*</td>
</tr>
<tr>
<td>Fearful vs. Neutral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left pSTS</td>
<td>–.25</td>
<td>–.03</td>
<td>.20</td>
</tr>
</tbody>
</table>

*Note. FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus.

*p < .05. **p < .01. †Significant at the Bonferroni-corrected alpha level of p < .0042.
Figure 5.3 Z-statistic map indicating areas of reduced activation in schizophrenia patients compared to healthy controls for the neutral vs. scrambled contrast.

Note. Activation map is projected onto the average functional image in radiologic convention (i.e., the left hemisphere is on the viewer’s right), with coordinates in MNI space.

Figure 5.4 Z-statistic map indicating areas of reduced activation in unaffected relatives compared to healthy controls for the neutral vs. scrambled contrast.

Note. Activation map is projected onto the average functional image in radiologic convention (i.e., the left hemisphere is on the viewer’s right), with coordinates in MNI space.
Figure 5.5 Z-statistic map indicating areas of reduced activation in schizophrenia patients compared to healthy controls for the sad vs. scrambled contrast.

*Note.* Activation map is projected onto the average functional image in radiologic convention (i.e., the left hemisphere is on the viewer’s right), with coordinates in MNI space.

Figure 5.6 Z-statistic map indicating areas of reduced activation in unaffected relatives compared to healthy controls for the sad vs. scrambled contrast.

*Note.* Activation map is projected onto the average functional image in radiologic convention (i.e., the left hemisphere is on the viewer’s right), with coordinates in MNI space.
Figure 5.7 Z-statistic map indicating areas of greater activation in schizophrenia patients compared to unaffected relatives for the angry vs. scrambled contrast.

Note. Activation map is projected onto the average functional image in radiologic convention (i.e., the left hemisphere is on the viewer’s right), with coordinates in MNI space.

Figure 5.8 Z-statistic map indicating areas of greater activation in unaffected relatives compared to healthy controls for the fearful vs. neutral contrast.

Note. Activation map is projected onto the average functional image in radiologic convention (i.e., the left hemisphere is on the viewer’s right), with coordinates in MNI space.
Figure 5.9 Z-statistic map indicating areas of greater activation in unaffected relatives compared to schizophrenia patients for the fearful vs. neutral contrast.

**Note.** Activation map is projected onto the average functional image in radiologic convention (i.e., the left hemisphere is on the viewer’s right), with coordinates in MNI space.
References


http://www.fmrib.ox.ac.uk/analysis/techrep/tr07ja1/tr07ja1.pdf

normalisation (Report No. TR07JA2). Retrieved from FMRIB Analysis Group:
http://www.fmrib.ox.ac.uk/analysis/techrep/tr07ja2/tr07ja2.pdf


Jenkinson, M., Bannister, P., Brady, J. M., & Smith, S. M. (2002). Improved optimization for the


doi:10.1093/schbul/15.4.559

doi: 10.1016/j.psychres.2014.01.023

doi:10.1176/appi.ajp.160.10.1768


Murray, R. J., Brosch, T., & Sander, D. (2014). The functional profile of the human amygdala in affective processing: Insights from intracranial recordings. *Cortex*. Advance online publication. doi:10.1016/j.cortex.2014.06.010


Appendix A: Examples of Stimuli

Figure A1 Examples of each stimulus category for the passive viewing fMRI task of facial emotion perception
Appendix B: Details of the Functional Localizer Task and Region of Interest Analyses

A functional region of interest (ROI) approach was used in order to investigate neural activation in functionally specified regions known to be involved in facial emotion perception. This approach is advantageous because it facilitates the identification of regions based on their functional response profiles, such that regions that are functionally similar yet anatomically variable across individuals (e.g., regions comprising the system for face perception) can be accurately pooled together across participants. In addition, this approach increases statistical power by constraining statistical analyses to the ROIs instead of over the entire brain, which requires corrections to control for the number of multiple comparisons performed (Saxe, Brett, & Kanwisher, 2006). While this approach also has potential limitations, such as the assumption of context-invariance of the neurons comprising the functionally defined ROI, the assumption of a homogenous response profile across voxels within the ROI such that they can be averaged together, and the possibility that localizer tasks may not successfully define ROIs for every participant (Friston, Rotshtein, Geng, Sterzer, & Henson, 2006), the functional ROI strategy is a powerful approach for constraining analyses to hypothesis-relevant regions and combining these regions across participants using functional rather than anatomical criteria.

Functional localizer task description

Participants completed a dynamic functional localizer task (Fox, Iaria, & et al., 2009) in which they viewed video-clips of either nonliving objects (e.g., candle burning, fan spinning) or dynamic displays of facial expressions (e.g., a face changing from neutral to happy) presented in separate blocks. Participants were required to perform a “one-back” task in which they pressed a response-key if the presented video-clip was identical to the previously viewed clip. Eight blocks of objects and eight blocks of faces were presented in a counterbalanced order. Each block
contained a series of six video-clips (five original and one repeated) presented for 2000 ms. Each block began and ended with a fixation block displaying a fixation cross presented at the center of an otherwise blank screen. The total task time was 396 s.

ROI analyses

Model fitting for the functional localizer task and the creation of ROI masks was carried out by Aiden E. Arnold. Standard model fitting was performed for each participant using time-series regression and implemented by FILM with local autocorrelation correction (Woolrich et al., 2001). The model included the faces and objects blocks as predictors, with fixation block as an implicit baseline. The boxcar function for each predictor was convolved with a double gamma hemodynamic response function, and contrasts of faces vs. objects were performed at the single-subject level. Resulting statistics images were thresholded using a cluster forming threshold of $z > 2.3$ and significance threshold of $p < .05$ corrected for whole-brain multiple comparisons using GRF-theory.

For each participant, ROIs were defined for three bilateral regions of the core system for face perception (Haxby et al., 2002), selected a priori. Face-sensitive voxels along the lateral portion of the fusiform gyrus were identified as the fusiform face area (FFA). The occipital face area (OFA) was identified by face-sensitive voxels on the lateral surface of the inferior occipital gyrus. Face-related voxels on the posterior portion of the superior temporal sulcus were designated as pSTS. The amygdala, part of the extended system for face perception (Haxby et al., 2002), was also selected a priori and defined by face-sensitive voxels in this region (Fox, Iaria, et al., 2009). A flexible statistical threshold was used for each subject and ROI in order maximize the number of ROIs identified. For ROIs not identified at the a priori family-wise error-corrected threshold of $p < .05$, the statistical threshold was lowered by using the more
liberal False Discovery Rate (FDR) correction at a threshold of \( p < .05 \), or an uncorrected \( p < .05 \) threshold if ROIs were not identified at the FDR threshold. Binary ROI masks were then created from each subjects’ ROIs using the xjView toolbox v8.12 (www.alivelearn.net/xjview8) to be used for the ROI analysis of the facial emotion perception data. See Figure B1 for representative images of each ROI.

For each participant, \( z \)-statistic images from the facial emotion perception contrasts (see whole-brain analyses) were multiplied by the binary ROI masks, and the mean \( z \)-value within each ROI was then averaged across participants at the group level. Group differences at each ROI for each contrast were assessed using one-way analysis of variance (ANOVA) and followed up with planned pairwise comparisons. Independent \( t \)-tests were used instead of pairwise comparisons when the homogeneity of variance assumption was violated.

References


Figure B1 Representative images of each region of interest

Note. FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus
Appendix C: ROI Results for the Supplemental Analyses

A  Weighted average of facial expressions vs. scrambled faces

B  Weighted average of emotional faces vs. neutral faces

Note. Region of interest (ROI) z-scores for the (A) weighted average of facial expressions vs. scrambled faces and (B) weighted average of emotional faces vs. neutral faces contrasts.

SCZ = schizophrenia patients; REL = healthy relatives; CTL = healthy controls. R = right; L = left; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus.

*p < .05. **p < .01.
Appendix D: Within-Group Results for the Whole-Brain Analyses

Facial expressions vs. scrambled faces

Within groups, the contrasts comparing facial expressions to scrambled faces revealed a distributed pattern of activation underlying the perception of facial emotions (Table D1). This network was most extensive for healthy controls, for example, the angry vs. scrambled contrast revealed activation in visual areas (bilateral OFA, FFA, calcarine cortex, lingual gyrus), temporal areas (bilateral pSTS, middle temporal gyrus), the parietal association cortex (left angular gyrus, supramarginal gyrus), motor regions (bilateral superior frontal gyrus, juxtapositional lobule), and the prefrontal cortex (left middle and inferior frontal gyri, frontal operculum, and orbitofrontal cortex). The supplemental analyses contrasting the weighted average of facial expressions vs. scrambled faces revealed that controls also activated limbic regions (bilateral amygdala, left hippocampus) (Appendix E).

In contrast, schizophrenia patients’ activation for facial expressions relative to scrambled faces was restricted to occipital regions (bilateral lingual gyrus, calcarine cortex, and cuneus), and relatives were not found to have any significant activation for any of the contrasts. However, healthy controls displayed a similarly limited pattern of activation for several contrasts (e.g., sad vs. scrambled), and no activation for other contrasts (e.g., fearful vs. scrambled).

Emotions faces vs. neutral faces

The contrasts between facial emotions and neutral faces revealed a pattern of activation that included both regions present in the comparison of facial expressions to scrambled faces, as well as unique regions (Table D1). For example, for the fearful vs. neutral contrast, relatives had significant activation in visual areas (left OFA, FFA; bilateral lingual gyrus, occipital pole), temporal areas (left pSTS, middle temporal gyrus), parietal association areas (left angular gyrus,
supramarginal gyrus), and prefrontal regions (left inferior frontal gyrus; bilateral superior frontal gyrus, frontal pole). The supplemental analyses contrasting the weighted average of facial emotions vs. neutral faces also revealed activation in left insula and left orbitofrontal cortex, as well as the left temporal pole (Appendix E).

The only contrast to display significant activation in the schizophrenia group was the angry vs. neutral contrast, which revealed a cluster extending bilaterally through visual areas including OFA, FFA, and lingual gyrus, as well as the left occipital pole.

No significant within-group activation was found for the control group for any of the contrasts between facial emotions and neutral faces.
Table D1 Significant within-group activation results

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Regions Within Each Cluster</th>
<th>Voxels</th>
<th>Max z-Statistic</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angry vs. Scrambled</strong></td>
<td>L FFA; L posterior supramarginal gyrus; L angular gyrus; L pSTS; L temporo-occipital middle temporal gyrus; L OFA; L occipital pole R FFA; R pSTS; R temporo-occipital middle temporal gyrus; R OFA R/L lingual gyrus; R/L calcarine cortex R/L superior frontal gyrus; R/L juxtapositional lobule L middle frontal gyrus; L Frontal operculum; L inferior frontal gyrus; L orbitofrontal cortex</td>
<td>3018</td>
<td>4.05</td>
<td>-42</td>
<td>-52</td>
<td>-20</td>
</tr>
<tr>
<td><strong>CTL</strong></td>
<td></td>
<td>2630</td>
<td>4.6</td>
<td>42</td>
<td>-46</td>
<td>-26</td>
</tr>
<tr>
<td><strong>SCZ</strong></td>
<td>R/L calcarine cortex; R/L lingual gyrus</td>
<td>1661</td>
<td>3.72</td>
<td>2</td>
<td>-78</td>
<td>2</td>
</tr>
<tr>
<td><strong>Fearful vs. Scrambled</strong></td>
<td></td>
<td>1620</td>
<td>4.13</td>
<td>0</td>
<td>12</td>
<td>58</td>
</tr>
<tr>
<td><strong>SCZ</strong></td>
<td>R/L lingual gyrus; R/L calcarine cortex; R/L cuneus</td>
<td>1180</td>
<td>3.76</td>
<td>-38</td>
<td>30</td>
<td>4</td>
</tr>
<tr>
<td><strong>Happy vs. Scrambled</strong></td>
<td></td>
<td>1662</td>
<td>4.37</td>
<td>10</td>
<td>-78</td>
<td>2</td>
</tr>
<tr>
<td><strong>Neutral vs. Scrambled</strong></td>
<td></td>
<td>1173</td>
<td>3.79</td>
<td>-10</td>
<td>-68</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neutral vs. Scrambled</strong></td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Angry vs. Neutral</strong></td>
<td></td>
<td>3518</td>
<td>3.76</td>
<td>-16</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td><strong>REL</strong></td>
<td>R/L calcarine cortex; R/L lingual gyrus; R/L cuneus</td>
<td>3328</td>
<td>3.93</td>
<td>18</td>
<td>-68</td>
<td>4</td>
</tr>
<tr>
<td><strong>Sad vs. Scrambled</strong></td>
<td></td>
<td>1101</td>
<td>4.21</td>
<td>-52</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td><strong>REL</strong></td>
<td>L inferior frontal gyrus; L orbitofrontal cortex; L frontal operculum cortex; L insula</td>
<td>2827</td>
<td>3.49</td>
<td>-30</td>
<td>-86</td>
<td>-16</td>
</tr>
<tr>
<td><strong>Fearful vs. Neutral</strong></td>
<td>R/L OFA; R/L FFA; R/L lingual gyrus; L occipital pole</td>
<td>2331</td>
<td>4.29</td>
<td>-54</td>
<td>-26</td>
<td>-6</td>
</tr>
<tr>
<td><strong>REL</strong></td>
<td>L posterior middle temporal gyrus; L pSTS; L angular gyrus, L posterior supramarginal gyrus L inferior frontal gyrus R/L lingual gyrus; R/L occipital pole; L FFA; L OFA R/L superior frontal gyrus; R/L frontal pole</td>
<td>2038</td>
<td>4.38</td>
<td>-52</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td><strong>Sad vs. Neutral</strong></td>
<td></td>
<td>1839</td>
<td>3.91</td>
<td>-4</td>
<td>-78</td>
<td>-6</td>
</tr>
<tr>
<td><strong>REL</strong></td>
<td></td>
<td>1144</td>
<td>3.82</td>
<td>-4</td>
<td>36</td>
<td>54</td>
</tr>
<tr>
<td><strong>Happy vs. Neutral</strong></td>
<td></td>
<td>1394</td>
<td>3.6</td>
<td>-4</td>
<td>-78</td>
<td>-4</td>
</tr>
<tr>
<td>Contrast</td>
<td>Regions Within Each Cluster</td>
<td>Voxels</td>
<td>Max z-Statistic</td>
<td>x</td>
<td>y</td>
<td>z</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------</td>
<td>--------</td>
<td>-----------------</td>
<td>----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Sad vs. Neutral</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Note. SCZ = schizophrenia patients; REL = healthy relatives; CTL = healthy controls. R = right; L = left; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus. Region labels were obtained through visual inspection and from the Harvard-Oxford probabilistic structural atlases. Voxels are the number of activated voxels per cluster. x, y, z are MNI coordinates for the peak of each cluster.*
Appendix E: Whole-Brain Activation Results for the Supplemental Analyses

<table>
<thead>
<tr>
<th>Contrast</th>
<th>Regions Within Each Cluster</th>
<th>Voxels</th>
<th>Max Z-Statistic</th>
<th>x</th>
<th>y</th>
<th>z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expressions&lt;sup&gt;a&lt;/sup&gt; vs. Scrambled</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CTL&gt;REL</td>
<td>L occipital pole; L OFA; L FFA; L cuneus</td>
<td>2418</td>
<td>3.6</td>
<td>-14</td>
<td>-94</td>
<td>-2</td>
</tr>
<tr>
<td>SCZ&gt;REL</td>
<td>R/L anterior cingulate; R/L paracingulate; R frontal pole; R superior frontal gyrus</td>
<td>1393</td>
<td>3.44</td>
<td>0</td>
<td>34</td>
<td>32</td>
</tr>
<tr>
<td>CTL</td>
<td>R/L cuneus, R/L calcarine cortex; R/L lingual gyrus; L pSTS; L angular gyrus; L OFA; L FFA</td>
<td>3849</td>
<td>4.17</td>
<td>4</td>
<td>-78</td>
<td>0</td>
</tr>
<tr>
<td>Emotions&lt;sup&gt;b&lt;/sup&gt; vs. Neutral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>REL&gt;SCZ</td>
<td>L inferior frontal gyrus; L insula; L putamen; L orbitofrontal cortex; L temporal pole</td>
<td>1491</td>
<td>3.82</td>
<td>-54</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>REL</td>
<td>L inferior frontal gyrus; L insula; L orbitofrontal cortex; L temporal pole</td>
<td>1506</td>
<td>4.38</td>
<td>-54</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>R/L lingual gyrus; L FFA</td>
<td>1403</td>
<td>4.2</td>
<td>-6</td>
<td>-78</td>
<td>-8</td>
</tr>
<tr>
<td></td>
<td>L angular gyrus; L OFA</td>
<td>974</td>
<td>3.75</td>
<td>-48</td>
<td>-58</td>
<td>20</td>
</tr>
</tbody>
</table>

Note. SCZ = schizophrenia patients; REL = healthy relatives; CTL = healthy controls. R = right; L = left; FFA = fusiform face area; OFA = occipital face area; pSTS = posterior superior temporal sulcus. Region labels were obtained through visual inspection and from the Harvard-Oxford probabilistic structural atlases. Voxels are the number of activated voxels per cluster. x, y, z are MNI coordinates for the peak of each cluster.

<sup>a</sup>Expressions = the weighted average of angry, fearful, happy, neutral, and sad trials. <sup>b</sup>Emotions = the weighted average of angry, fearful, happy, and sad trials.