Running Head: Schizophrenia Polygenic Risk and Emotion Perception

Title: Association between schizophrenia polygenic risk and neural correlates of emotion perception.

Authors: Ilvana Dzafic[*a,b], Hana Burianová[b,c], Sathish Periyasamy[a,d], Bryan Mowry[a,d]

[a]Queensland Brain Institute, University of Queensland, Brisbane, Australia

[b]Centre for Advanced Imaging, University of Queensland, Brisbane, Australia

[c]Department of Psychology, Swansea University, Swansea, United Kingdom

[d]Queensland Centre for Mental Health Research, Brisbane, Australia

[*] **Correspondence should be addressed to:**
Ilvana Dzafic
Queensland Brain Institute,
University of Queensland,
Brisbane, QLD, 4072, AUSTRALIA
i.dzafic@uq.edu.au

Abstract

The neural correlates of emotion perception have been shown to be significantly altered in schizophrenia (SCZ) patients as well as their healthy relatives, possibly reflecting genetic susceptibility to the disease. The aim of the study was to investigate the association between SCZ polygenic risk and brain activity whilst testing perception of multisensory, dynamic emotional stimuli. We created SCZ polygenic risk scores (PRS) for a sample of twenty-eight healthy individuals. The PRS was based on data from the Psychiatric Genomics Consortium and was used as a regressor score in the neuroimaging analysis. The results of a multivariate brain-behaviour analysis show that higher SCZ PRS are related to increased activity in brain regions critical for emotion regulation during the perception of threatening (angry) emotions. These results suggest that individuals with higher SCZ PRS may *over-activate* the neural correlates underlying emotion during perception of threat, perhaps due to an increased experience of fear or neural inefficiency in emotion-regulation areas in individuals who have higher genetic susceptibility to SCZ. Moreover, over-recruitment of emotion regions might function as a compensation to maintain normal emotion regulation during threat perception. If replicated in larger studies, these findings may have important implications for understanding the neurophysiological biomarkers relevant in SCZ.

Keywords: schizophrenia; polygenic risk; fMRI; dynamic emotion; threat; emotion regulation.

1.) Introduction

Schizophrenia (SCZ) is a highly debilitating and heritable mental illness, characterized by impairment in diverse abilities spanning perception, reasoning, and social cognition (de Jong et al., 2013; Green et al., 2004). Evidence suggests that the SCZ-related impairment in these abilities may be due to the dynamic interplay between genes and brain (Martin et al., 2014; Roffman et al., 2006). Current estimates from twin and family studies put the heritability of SCZ at 81% (Wahlstrom et al., 1986), which has led to large collaborative efforts to identify genes able to explain this heritability. However, to date, the identified genes explain only 7% of the liability to SCZ (Ripke et al., 2014). As SCZ is considered an umbrella term, likely encompassing a large number of aetiologies, one approach to explaining the missing heritability is to search for intermediate traits that lie on a causal pathway between the genotype and clinical phenotype. An endophenotype is described as an intermediate trait that theoretically should be measurable, heritable, and state-independent, with neurophysiological and neurocognitive qualities (Cannon and Keller, 2006; Mowry and Gratten, 2013). One of these neurocognitive intermediate traits is emotion perception, as it has well-established evidence of impairment and aberrant underlying brain function in SCZ (Namiki et al., 2007; Romero-Ferreiro et al., 2016; Vai et al., 2015). Robust evidence has emerged identifying emotion perception as a viable endophenotype for SCZ, as deficits in emotion perception are heritable, associated with SCZ risk genes, and apparent before illness onset (Bediou et al., 2007; Germine et al., 2016). It is thus of importance to investigate the specific processes and neurobiological underpinnings of emotion perception and their relationship with risk genes, as such research would lead to a clearer understanding of the pathway from genotype to clinical phenotype.

The endophenotypic role of emotion perception in schizophrenia has been highlighted with evidence of robust deficits in SCZ, which persist throughout the course of illness and

which are also present in healthy individuals with high SCZ susceptibility (Behere, 2015). In a recent review, Behere (2015) posits that emotion recognition difficulties are trait markers for SCZ, particularly difficulties recognizing threatening emotions, such as anger, and misattribution of threat onto ambiguous facial expressions (Behere, 2015). Impaired threat processing was found to be a stable deficit, present in both acute and remission phases of SCZ; however, these deficits were particularly heightened in those with psychotic symptoms. Thus, aberrant processing of facial expressions could potentially be linked to development of psychopathology. In support of this notion, a number of SCZ common genetic risk variants have been reported to be associated with emotion and facial processing ability and its underlying neural circuitry (Greenwood et al., 2011; Martin et al., 2014). Moreover, previous research investigating genetic susceptibility to SCZ has identified that healthy relatives of those with SCZ have impaired emotion perception, such as misattributing threat onto neutral expressions (Eack et al., 2010). In addition, research shows that healthy individuals with high SCZ risk have altered activity in emotion neural correlates, such as frontal regions, anterior cingulate gyrus, nucleus accumbens, amygdala, and hippocampus (Phillips and Seidman, 2008). Considering these abovementioned findings, in the current study we hypothesized that SCZ genetic risk in healthy individuals would be associated with aberrant brain processing during emotion perception, particularly for threatening emotions.

With large genome-wide association studies (GWAS) identifying over 100 common risk variants significantly associated with SCZ (Ripke et al., 2014), a new direction in the field has been to consider the polygenic nature of SCZ by quantifying the combined effect of variants into a polygenic risk score (PRS). Recently, a large polygenic study has shown that deficits in emotion recognition are significantly associated with SCZ polygenic risk across development, supporting the notion that impaired processing of facial expressions may constitute a link between genetic risk for SCZ and development of psychosis (Germine et al.,

2016). Notwithstanding the important findings from this study, Germine and colleagues utilized emotion tasks with static pictures as stimuli, consequently examining different underlying mechanisms compared to naturalistic, dynamic displays of emotion (Arsalidou et al., 2011; Palumbo and Jellema, 2013). As the field is moving towards more ecologically valid tasks, it is important to assess emotion perception using dynamic, audio-visual displays in order to gauge real-life emotion processing. In addition, it may be important to evaluate different contexts of emotion recognition; for example, when a certain emotion is expected or unexpected. Recent evidence shows that individuals with SCZ have reduced precision in their prior expectations, which impairs perception (Adams et al., 2016); thus, it seems critical to explore the influence of SCZ genes on the underlying processes driving emotion perception impairment.

The impact of SCZ polygenic risk on emotion recognition has, thus far, been examined only at the behavioral level, with no study to date investigating the influence on brain function underlying emotion perception. As robust evidence highlights that SCZ is a disorder of aberrant brain function (Coyle et al., 2016; Liang et al., 2006), the objective of this study was to investigate the association between polygenic risk of SCZ in healthy individuals and the neural correlates of emotion perception. A recently new field of study, 'imaging genetics' has focused on the neurobiological intermediate traits of SCZ, informed by neuroimaging. Imaging genetics allows us to map the neural activity of abilities, such as emotion perception, as a function of genotype. Using the imaging genetics technique, a number of genome-wide significant risk variants have been investigated with respect to their association with the emotion brain network. The findings reveal that risk alleles of certain candidate genes are associated with increased and inefficient connectivity between frontal regions and limbic regions, which play a key role in emotion regulation and emotional learning (Curcic-Blake et al., 2012; Mothersill et al., 2013; Surguladze et al., 2012). As

schizophrenia has a complex polygenetic architecture, recent imaging genetic studies have investigated the cumulative effects of risk variants (applying the polygenic risk model) on brain function (Birnbaum and Weinberger, 2013). Imaging polygenic studies have found associations between SCZ genetic risk and white matter volume (Terwisscha van Scheltinga et al., 2013), as well as neural inefficiency in frontal regions (Lancaster et al., 2016; Walton et al., 2013). However, no imaging genetic study to date has explored the association between polygenic risk of SCZ and the brain regions underlying emotion perception.

The objective of the current study was to investigate the association between polygenic risk of SCZ in healthy individuals and neural correlates of emotion perception, in different expectancy contexts. For this purpose, we used a previously validated Dynamic Emotion Perception (DEP) task (Dzafic et al., 2016), with increased ecological validity, three emotional conditions (anger, happiness, and neutral) expressed by an actor in an audio-visual video and two levels of expectation (congruency and incongruency with prior expectations). Our focus was on healthy individuals for the following reasons: (1) robust evidence shows that genetic risk for SCZ in healthy individuals influences emotion processing (Eack et al., 2010; Germine et al., 2016) and (2) healthy individuals present a cleaner sample, without the confounds of illness and medication, which affect brain function. For the polygenic risk scores (PRS) we used summary data from SCZ PGC2 (Ripke et al., 2014) to assess differences in brain activation during a functional magnetic resonance imaging (fMRI) scan. We conducted a multivariate analysis to characterize activity in brain regions that covaries with individual SCZ PRS during the DEP task. Based on the results of previous studies, we predicted that SCZ PRS would be associated with aberrant activity in neural correlates of emotion regulation and emotional learning (Curcic-Blake et al., 2012; Mothersill et al., 2013), such as frontal and limbic regions. Additionally, we predicted that schizophrenia PRS would have the strongest association with aberrant brain activity during the viewing of

threatening emotions, as perception of these types of emotions is most impaired in schizophrenia (Behere, 2015) and healthy relatives of those with SCZ (Eack et al., 2010).

2.) Methods

2.1. Participants

Twenty-eight Caucasian right-handed healthy controls (HC; mean age = 49.61, SD = 9.09, 18 male) were recruited from a population-based Australian sample. The ancestry of the sample was European. Screening was conducted over the phone prior to the recruitment, to confirm that participants had no history of eye disease, neurological disorders, metal implants, or current medication. The Mini International Neuropsychiatric Interview (M.I.N.I.) version 5.0.0 (Sheehan et al., 1997), was used to ensure that participants did not have current alcohol dependence and were not experiencing a major depressive episode. Intelligence quotient (IQ) was estimated using 2 subsets (vocabulary and matrix reasoning) of the Wechsler abbreviated scale of intelligence (WASI; Wechsler (1999). Participants were provided with an information sheet, which included a full description of the study and an MRI information sheet. Written informed consent was obtained. This research was approved by the West Moreton Hospital and Health Service, and The University of Queensland Human Research Ethics Committees.

2.2. Genotyping and quality control

Genotyping was conducted using Illumina OmniExpress-12 arrays containing > 712,000 markers for 12 controls and PsychChip arrays containing > 570,000 markers for 17 controls respectively. Standard quality control procedures for samples and markers were conducted using established protocols (Anderson et al., 2010). These two datasets were merged and single nucleotide polymorphisms (SNPs) were excluded if the minor allele

frequency was < 5%, if the call rate was < 97%, or if the χ2-test for Hardy–Weinberg Equilibrium had a *p*-value < 1e-06. After filtering, 220,707 variants were used for PRS analysis.

2.3. Generation of polygenic risk scores

SCZ genetic risk was estimated using publicly available results from an international GWAS of 34,241 SCZ cases and 45,604 controls (Schizophrenia Workgroup of the Psychiatric Genomics Consortium). SCZ PRS was calculated using the method described by the International Schizophrenia Consortium (Wray et al., 2014), implemented in the software PRSice v1.25: Polygenic Risk Score (Euesden et al., 2014). A list of SNPs in common between discovery and target samples was determined and subsequently clumped for linkage disequilibrium (R^2 < 0.2) across 500kb regions. This ensured that all SNPs included in each SCZ PRS model were independent. The SNP list, which included 12,897 SNPs was limited to those with association *p*-values less than the standard GWAS threshold for genome-wide significance (5×10^{-8}). Individual PRS were calculated using this SNP list (refer to Supplementary Table 2 in Ripke et al. (2014)). The PRS were normally distributed (Kolmogorov-Smirnov: p = 0.20) and did not contain any outliers. A power analysis was performed (R software: "pwr.r.test" function (1988)), yielding 80% power to observe a moderate effect (r = 0.5) of PRS on Blood-oxygen-level dependent (BOLD) during emotion perception (n = 28, α = 0.05, two-sided).

2.4. Dynamic emotion perception task

The Dynamic emotion perception (DEP) task involved viewing emotional audio-visual videos that were either congruent or incongruent with the emotional prior expectations. In the task, prior expectations were manipulated by displaying an emotion instruction cue

before the videos and by increasing the occurrence likelihood of emotional videos congruent with the emotion in the instruction. The DEP task consisted of forty-eight 3-second videos of a Caucasian female actor speaking different sentences in an emotional manner (either in an angry, happy, or neutral tone). The emotion instruction cues presented a still picture of the actor expressing an emotion, with the expressed emotion written in white text underneath the picture. There were 3 still pictures of the actor and, in each one, the actor expressed either an angry, happy, or neutral emotion. At the start of each block, the cue contained white text above the picture, instructing to make an "index finger press" for the target emotion (for further details, see Dzafic et al. (2016)).

2.5. Design

The experimental procedure consisted of nine experimental conditions: 3 emotion instruction cues (happy, angry or neutral) × 3 emotional videos (happy, angry or neutral). Each experimental block began with an instruction emotion cue (3 s), followed by six or nine sequences of trials consisting of an emotion cue (1 s), a black screen as the inter-stimulus interval (ISI; mean duration of 1s) and an emotional video clip (3 s). The ISI was jittered within a block, with a uniform distribution between 500ms and 1500ms, of either 6 × 200ms intervals (during blocks of 6 video clips) or 9 × 125ms intervals (during blocks of 9 video clips). Within a block of six video clips, there were four congruent and two incongruent video clips; and within a block of nine video clips, there were five congruent and four incongruent video clips.

The experiment was a mixed design, with the same emotion cues presented several times within a block (block design), but with varying emotional videos (alternating in emotional content) presented within a block (event-related design). 'Congruent' videos matched the emotional content of the cues, whereas 'incongruent' videos did not. The

behavioral and fMRI analyses involved the conditions ‘angry congruent’ (angry cue + angry video), ‘angry incongruent’ (happy/neutral cue + angry video), ‘happy congruent’ (happy cue + happy video), ‘happy incongruent’ (angry/neutral cue + happy video), ‘neutral congruent’ (neutral cue + neutral video), ‘neutral incongruent’ (happy/angry cue + neutral video). The videos within a block were randomized so that the appearance of congruent or incongruent video clips could not be predicted. The emotion blocks were counterbalanced between runs, as were the runs between participants, using the Balanced Latin Squares method.

2.6. Procedure

The participants were asked to respond to the videos to indicate if the emotion presented in the instruction cue matched the emotion expressed in the video. Specifically, participants were told to press the button with their index finger when the video was congruent with the instruction cue and press with their middle finger when it was not. All responses occurred within 3 seconds during the videos, giving sufficient time for the participant to respond. Accuracy and reaction times (RTs) were recorded for each trial.

Prior to the fMRI experiment, participants were trained with a practice task outside the MRI scanner. Both the practice task and fMRI task were presented using E-Prime 2.0 software (https://www.pstnet.com/eprime.cfm, 2013; Schneider et al., (2012)) on a Windows computer screen. The practice task consisted of 9 blocks and feedback was given if the correct/incorrect button was pressed. The goal was to ensure that participants understood the aim of the task and that the finger response became automated outside the scanner. During the fMRI experiment the DEP task was seen by participants through a tilted mirror attached to the head coil on the MRI scanner. Responses were made on a custom-built MRI-compatible response box. Participants were instructed to respond as quickly and as accurately as possible and no feedback was given in the actual experiment. After the fMRI experiment,

participants completed the two questionnaires: WASI (Wechsler, 1999) and Mayer-Salovey-Caruso Emotional Intelligence Test (MSCEIT; Mayer et al. (2003)), in a testing room outside the MRI scanner. The practice task, fMRI task, and questionnaires were completed at the Centre for Advanced Imaging, University of Queensland 3T scanner facility.

2.7. MRI procedure and preprocessing

Structural and functional MRI images were acquired by a 3T Siemens Magnetom TrioTim system using a 12-channel head coil. The scans collected for each subject, in a session were as follows: localizer, T1-weighted anatomical image MP2RAGE sequence (repetition time (TR): 1900 ms, echo time (TE): 2.32 ms, resolution: 1mm^3, FoV: 230 mm, 196 slices), T2* weighted echo-planar sequence (TR: 3000 ms, TE: 30 ms, resolution: 2.5 mm^3, slices: 46, FoV: 192 mm), DWI (TR: 8400 ms, TE: 100 ms, resolution: 2.3 mm × 2.3 mm × 2.5 mm, slices: 60, FoV: 300 mm, b-value: 2000 s/mm^2, directions: 64), and resting-state (TR: 3000 ms, TE: 30 ms, resolution: 2.5 mm^3, slices: 46, FoV: 192 mm). The total scanning time per session was 45 minutes.

Standard preprocessing of the images was carried out using SPM8 (Welcome Department of Imaging Neuroscience, UCL, UK, http://www.fil.ion.ucl.ac.uk/spm/ spm5.html). The preprocessing steps were as follows: slice timing on the functional images to correct for differences in slice acquisition times within each volume using the middle slice as reference; realignment (estimate and reslice) on the functional images to correct for inter-scan movement within each run (no participant was excluded for excessive movement (defined as >3 mm translation, >2 degrees rotation); co-registration of the functional and structural images; segmentation of the structural image with heavy regularisation (0.1) recommended for MP2RAGE sequence; normalization of the resliced images into a standardized,

stereotaxic space (according to the Montreal Neurological Institute template); and smoothing of normalized images with 6mm full-width-at-half-maximum isotropic Gaussian kernel.

2.8. Data analysis

We conducted the fMRI analyses using a multivariate approach, Partial least-squares (PLS), to examine the direct association between brain activity and PRS. PLS investigates the distributed patterns of neural activity and is optimally suited for complex cognitive functions (McIntosh and Lobaugh, 2004), such as naturalistic emotion perception, which engages a widespread and interactive brain network (Arsalidou et al., 2011; Vuilleumier and Pourtois, 2007). PLS identifies the fundamental relations (latent variables: LVs) between brain activity, experimental conditions, and individual differences variables (such as PRS) that account for maximum covariance in the data. Similar to principal component analysis, PLS decomposes the data into orthogonal LVs by conducting singular value decomposition (SVD) (McIntosh et al., 2004). For each LV, "brain scores" are computed for each participant, which indicate the degree to which each participant shows the pattern of brain activity identified. Each LV consists of three components: singular values (significance for a given LV), voxel saliences (spatiotemporal activity for a given LV), and task saliences (degree to which each condition is related to the brain-PRS correlations within the given LV).

In order to examine the relationship between brain and PRS as a function of experimental condition, we included fMRI data during each video condition in a data matrix cross-correlated with the PRS. We isolated activity during the videos by conducting the analysis across five TRs (TR 0 – TR 5) starting at the onset of the video clips. Activity at each time point was normalized to the first TR (labelled TR 0 in the figures). For all analyses, we ran 1000 permutations (Le Floch et al., 2012; McIntosh et al., 1996) to determine significant LVs at $p < 0.001$. In addition, we ran 100 bootstraps, estimating the standard

errors of the salience for each voxel in order to assess the reliability and robustness of each voxel's contribution to a pattern of brain activity. We used the mean-centering approach in PLS, which involves subtracting the grand mean of the data matrix from the task means. We restricted the bootstrap ratio threshold to ± 3 ($p < 0.001$) and reported areas with a cluster size of 100 or more voxels. Confidence intervals (95%) were calculated from the bootstrap procedure; for the mean brain scores in each condition across the five TRs, significant differences between conditions were determined by a lack of overlap in the confidence intervals.

3.) Results

3.1 Demographic and behavioural measures

Participants' mean accuracy percentage (performance) scores on the DEP task are presented in Table 1. We performed Pearson's correlations to investigate associations between SCZ PRS and participant demographics and performance on the DEP task. There were no significant associations between SCZ PRS and age, IQ or performance on the different conditions of the DEP task, $p > 0.08$, in all cases (see Table 2). In addition, we performed Independent t-tests to examine the gender difference for SCZ PRS and performance on the DEP task. There were no significant differences associated with gender on SCZ PRS or performance on DEP conditions: Angry Congruent, Angry Incongruent, Happy Incongruent, Neutral Congruent and Neutral Incongruent, $p > 0.11$, in all cases. There was a significant difference associated with gender on performance during the DEP condition Happy Congruent, t (10.36) = 2.33, $p = 0.04$.

[Please insert Table 1 & 2 here]

3.2. Schizophrenia PRS and neural correlates of dynamic emotion perception

The first LV ($p < 0.001$) accounted for 30.98% of covariance in the data. The LV differentiated brain activity during congruent angry conditions and congruent/incongruent happy conditions, based on PRS. Specifically, PRS correlated positively with brain activity during perception of angry videos congruent with prior expectations, and PRS correlated negatively with brain activity during perception of happy videos congruent and incongruent with prior expectations (see Fig. 1). The brain regions activated include the bilateral dorsolateral prefrontal cortex (dlPFC), dorsomedial prefrontal cortex (dmPFC), bilateral inferior frontal gyri, bilateral supplementary motor area, bilateral amygdala, right anterior cingulate gyrus, right anterior insula (rAI), right temporoparietal junction (TPJ), bilateral precuneus, superior temporal gyrus, left hippocampus and right thalamus (see Table 3). Activation in these areas is critical for emotional regulation (Etkin et al., 2015; Frank et al., 2014; Kohn et al., 2014).

[Please insert Figure 1 & Table 3 here]

4.) Discussion

The aim of the current study was to investigate the association between SCZ polygenic risk and brain function in healthy participants during emotion perception. To our knowledge, this is the first imaging genetics study to investigate the association of SCZ polygenic risk on emotion perception. The results show a positive correlation between SCZ PRS and increased brain activity during anger (threat) perception, and a negative correlation between SCZ PRS and decreased brain activity during perception of happiness. The pattern of the activated brain regions involved emotion processing neural correlates, such as prefrontal regions, parietal cortex, anterior cingulate, amygdala and right anterior insula

(rAI). These results suggest that individuals with higher SCZ PRS may over-activate emotion areas during perception of threat, particularly when threat is congruent with prior expectations. The over-activation in emotion brain regions may reflect an increased experience of fear or neural inefficiency in regulatory regions in those with a greater genetic risk for SCZ, resulting in more effort to regulate the experience of threat.

Our findings provide support for a link between SCZ common variant genetic risk profiles and aberrant activity in neural correlates of emotion perception (Curcic-Blake et al., 2012; Mothersill et al., 2014). In our study, we demonstrate that when viewing threatening emotions, healthy individuals with greater SCZ genetic risk, had hyperactivity in regions such as the rAI and bilateral amygdala, both implicated in emotional reactivity and the signaling of salience and, consequently, the need to regulate (Phillips et al., 2003a); the dorsal prefrontal cortex (dPFC), which is critically involved in driving regulatory processes, such as attention, reasoning, and the representation of emotional associations (Kohn et al., 2014; Ochsner and Gross, 2005); the superior temporal gyrus, angular gyrus, and SMA, regions implicated in executing the regulatory processes initiated by dPFC (Kohn et al., 2014); the right anterior cingulate gyrus, a region critical in effortful error-related regulation (Bush et al., 2000); and finally, the left hippocampus, a region with a role in inhibiting negative emotions and response to threat (Gray and McNaughton, 2003). Although these emotion processing and regulation areas were recruited to a greater extent in those individuals with higher SCZ PRS, we did not find that their performance was better in discriminating emotions during the DEP task. Increased activation in these brain regions in the presence of no improvement in behavioural performance may indicate inefficient emotion regulation activity in those with higher SCZ PRS, particularly when viewing threatening emotions. Alternatively, increased activation in areas implicated in emotional reactivity and salience (such as the rAI and amygdalae) may indicate that those with higher SCZ PRS experienced more fear when

viewing threatening emotions compared to people with lower SCZ PRS. In comparison, viewing happy emotions was not related to increased activation in the emotion processing areas in those with higher PRS, furthermore individuals with lower PRS were found to have decreased activity in these emotion regions during the perception of happiness. This may be because regulation is found to be easier for happy emotions compared to threatening emotions (Kim and Hamann, 2007), and thus lesser engagement of emotion regulation neural correlates is required.

An integral component during emotion perception (Phillips et al., 2003b) is the ability to regulate your own emotions during the processing of others emotional expressions. Individuals with maladaptive emotion regulation and greater emotional reactivity have impaired recognition of emotional expressions (Swart et al., 2009). Emotion dysregulation is a core feature of SCZ (Ellgring and Smith, 1998; Kring and Werner, 2004). A recent review and meta-analysis shows that individuals with SCZ have global emotion regulation difficulties, engaging in maladaptive strategies to regulate their emotions (O'Driscoll et al., 2014). There is also behavioural and neurophysiological evidence that individuals with SCZ particularly struggle with regulating their experience of negative emotions, such as anger (Cohen and Minor, 2010; Strauss et al., 2013). Underlying the emotion regulation difficulties in SCZ is aberrant brain activity in regions such as the left vlPFC, inferior frontal gyrus, and anterior insula (van der Meer et al., 2014) and disconnection between frontal and limbic regions during regulation of negative emotion (Morris et al., 2012). A recent real-time fMRI study revealed that individuals with SCZ are able to improve their recognition of negative emotions by learning to regulate activation of the rAI (Ruiz et al., 2013), a region with a central role in emotion regulation (Gu et al., 2013). Therefore, aberrant neural activity during emotion regulation and a greater experience of fear during perception of angry expressions may provide an explanation for emotion recognition deficits in SCZ.

Our results seem to reflect that healthy individuals with higher genetic risk over-recruit the emotion processing areas either due to an increased experience of fear or an attempt to maintain normal emotion regulation during threat perception. Previous research supports this notion, with studies finding that healthy individuals with a greater risk of developing SCZ over-activate regulatory regions in order to effectively regulate their experience of negative emotions (Modinos et al., 2010; Mohanty et al., 2005). Interestingly, we found over-activity in emotion regions particularly during perception of threatening emotions that were *congruent* with prior expectations; in other words, threat that was expected. This finding may reflect that individuals with greater genetic risk for SCZ, similarly to individuals with SCZ, have reduced precision in prior expectations (Adams et al., 2016), and, therefore, have a greater sensory experience of threat and/or require more regulation to processes expected threat. Further examination and replication of these findings in larger studies may link emotion processing as a potential biomarker of SCZ pathophysiology, with important implications for risk identification, early intervention, and improving psychosocial therapy for SCZ.

4.1. Limitations

A major limitation of the current study is the sample size compared to other imaging genetic studies. Although we had sufficient power (80%) and observed robust effects, larger replication studies are needed to investigate the effects of SCZ PRS on neural activity underlying emotion perception. Nonetheless, we have incorporated methods to increase the power of this study by: (1) utilising the cumulative genetic risk approach, which increases the effect size of liability for SCZ compared to the candidate gene approach; (2) calculating and using the SCZ PRS as a regressor variable rather than a predictor score, and (3) basing our PRS on summary statistics from the most recent, large schizophrenia PGC2 (Ripke et al.,

2014) dataset (*n* = 34,241 SCZ cases; 45,604 controls), with resultant increased power and predictive capacity (Dudbridge, 2013).

4.2. Conclusions

Our results suggest that the alterations in neural activity during emotion perception identified previously in SCZ may be explained to a significant extent by common genetic variants. We observed associations between SCZ PRS and increased activity in the neural correlates of emotion processing during perception of threatening emotions. These results provide evidence that genetic risk for SCZ may be associated with an increased experience of fear and/or widespread neural inefficiency in emotion-regulation areas. When combined with other pathological factors, this neural inefficiency during emotion perception may increase risk for psychosis. In this study, we build on the work in imaging genetics by assessing how cumulative genetic susceptibility for SCZ influences emotion perception and related neural activity. We provide support for the PRS approach in delineating potential biomarkers for SCZ, and the potential to contribute to translational neuroscience efforts to improve risk identification, early intervention, and psychological treatments.

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Contributors

Author ID designed the paradigm, analysed the data and wrote the first draft of the manuscript. Authors HB and BM assisted in the design of the paradigm, author SP generated the polygenic risk scores. All authors contributed to and have approved the final manuscript.

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Conflict of Interest

The authors declare no competing financial interests.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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TABLE 1

Mean Accuracy Percentage Scores during the DEP task

	Mean (SD)
1. Angry Congruent accuracy (N = 28)	93.63% (7.66)
2. Angry Incongruent accuracy (N = 28)	96.55% (9.91)
3. Happy Congruent accuracy (N = 28)	97.29% (4.36)
4. Happy Incongruent accuracy (N = 28)	96.06% (9.62)
5. Neutral Congruent accuracy (N = 28)	97.25% (5.19)
6. Neutral Incongruent accuracy (N = 28)	97.33% (8.15)

Abbreviations: DEP = Dynamic Emotion Perception; N = sample size.

TABLE 2

Pearson's Correlation Matrix among Age, IQ, performance during the DEP task and SCZ PRS

	2.	3.	4.	5.	6.	7.	8.	9.
7. SCZ PRS (N = 28)	0.14	-0.34	0.34	0.18	0.07	0.20	0.12	0.00
8. Age (N = 28)	1	-0.11	-0.24	-0.09	-0.01	-0.03	-0.10	-0.11
9. IQ (N = 26)		1	0.04	-0.09	0.27	-0.06	-0.05	-0.06
10. Angry Congruent accuracy (N = 28)			1	.59**	.70**	.47*	.56**	.48**
11. Angry Incongruent accuracy (N = 28)				1	.65**	.93**	.91**	.96**
12. Happy Congruent accuracy (N = 28)					1	.62**	.61**	.63**
13. Happy Incongruent accuracy (N = 28)						1	.87**	.88**
14. Neutral Congruent accuracy (N = 28)							1	.86**
15. Neutral Incongruent accuracy (N = 28)								1

Abbreviations: DEP = Dynamic Emotion Perception; SCZ = schizophrenia; PRS = polygenic risk score; N = sample size. *$p < 0.05$, **$p < 0.01$.

TABLE 3

Brain region	Hem	BA	MNI coordinates			Voxels	BSR
			x	*y*	*z*		
LV1: Brain activity during emotion perception associated with SCZ PRS.							
dlPFC	B	6, 8	16	32	46	688	7.23
			-8	50	48	377	6.03
Precentral	R	6	34	-6	54	2509	6.11
dmPFC	L	6, 11	-4	36	34	1378	5.67
Inferior frontal	B	13, 47	32	14	-18	446	5.61
			-24	20	-22	209	4.64
SMA		31	-6	-12	48	2205	5.51
Amygdala	B		-20	-10	-24	360	8.26
			26	-12	-24	556	5.80
Posterior mid-cingulate	B	23, 24	8	-14	26	600	6.93
			-20	-14	44	369	6.51
Posterior Cingulate	L	30	-12	-66	16	911	6.00
Anterior Cingulate	R	24	8	34	4	335	5.82
Hippocampus	R		32	-16	-20	464	5.56
Middle occipital	L	19	-56	-68	-2	237	5.11
Cuneus	R	19	32	-80	30	281	4.63
Precuneus	B	7, 19	20	-44	62	3418	6.39
			-28	-74	48	790	6.07
Postcentral	B	3	32	-26	56	1354	6.05
			-48	-14	46	729	5.32
Temporoparietal junction	R	40	68	-26	34	231	5.32
Superior parietal lobule	R	7	26	-50	72	262	4.82
Thalamus Pulvinar	R		18	-34	16	1243	6.71
Insula	R	13	44	10	-6	210	6.17
Claustrum	R		42	-14	-8	1078	5.48
Caudate	R		4	24	-4	218	5.17
Globus Pallidus	L		-20	-16	-8	270	4.90
Middle temporal	B	39, 21	-58	-60	16	543	6.81
			60	-16	-26	271	5.45
Superior temporal	B	22, 41	-40	2	-20	550	5.86
			54	2	-4	371	4.64

Abbreviations: Hem = hemisphere; BA = Brodmann area; R = right; L = left; B = bilateral; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; SMA = supplementary motor area; BSR = bootstrap ratio; voxels = number of voxels (one voxel volume = 6 mm^3). All reported activations are ≥100 voxels (600 mm^3).

Figure Captions

Figure 1. Results of the behavioural PLS analysis, association between brain activity during emotion perception and schizophrenia polygenic risk scores. (Top panel) Whole-brain activity in emotion regulation regions, such as the prefrontal cortex, inferior frontal gyri, bilateral amygdala and right anterior insula. (Bottom Panel) Correlations between brain scores representing activity in the regions displayed in the top panel and polygenic risk scores, with positive correlations during the angry congruent conditions and negative correlations during the happy congruent and incongruent conditions. Asterisk denote a significant correlation based on 95% confidence intervals calculated from the bootstrap procedure, Angry Congruent [0.50, 0.84], Happy Congruent [-0.89, -0.66], Happy Incongruent [-0.89, -0.57]. Moderate effect sizes with 80% power were reported as significant.