Facial Emotion Recognition in Psychosis and Associations With Polygenic Risk for Schizophrenia: Findings From the Multi-Center EU-GEI Case–Control Study

Giada Tripoli*[,1,2], Diego Quattrone[3–5], Laura Ferraro[1,©], Charlotte Gayer-Anderson[6,©], Caterina La Cascia[1], Daniele La Barbera[1], Crocettarachele Sartorio[1], Fabio Seminerio[1], Victoria Rodriguez[2], Ilaria Tarricone[7], Domenico Berardi[8], Stéphane Jamain[9,©], Celso Arango[10], Andrea Tortelli[11], Pierre-Michel Llorca[12], Lieuwe de Haan[13], Eva Velthorst[13,14], Julio Bobes[15], Miquel Bernardo[16], Julio Sanjuán[17], Jose Luis Santos[18], Manuel Arrojo[19], Cristina Marta Del-Ben[20], Paulo Rossi Menezes[21], Els van der Ven[22,23], Peter B. Jones[24,25], Hannah E. Jongsma[26], James B. Kirkbride[26,©], Sarah Tosato[27], Antonio Lasalvia[28,©], Alex Richards[29,©], Michael O'Donovan[29], Bart P.F. Rutten[22], Jim van Os[1,22,30], Craig Morgan[6], Pak C. Sham[3,31], Marta Di Forti[3,4], Robin M. Murray[2], and Graham K. Murray[24,25,32]

[1]Department of Biomedicine, Neuroscience, and Advanced Diagnostics, University of Palermo, Palermo, Italy; [2]Department of Psychosis Studies, Institute of Psychiatry, Psychology, and Neuroscience, King's College London, London, UK; [3]Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [4]National Institute for Health Research (NIHR) Maudsley Biomedical Research Centre, South London and Maudsley NHS Foundation Trust, King's College London, London, UK; [5]Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Mannheim, Germany and National Institute for Health Research (NIHR) Mental Health Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, UK; [6]Department of Health Service and Population Research, Institute of Psychiatry, King's College London, London, UK; [7]Department of Medical and Surgical Science, Psychiatry Unit, Alma Mater Studiorum Università di Bologna, Bologna, Italy; [8]Department of Biomedical and NeuroMotor Sciences, Psychiatry Unit, Alma Mater Studiorum Università di Bologna, Bologna, Italy; [9]Institut National de la Santé et de la Recherche Médicale, Faculté de Médecine, Université Paris-Est, Creteil, France; [10]Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health. Hospital General Universitario Gregorio Marañón, School of Medicine, Universidad Complutense, IiSGM, CIBERSAM, Madrid, Spain; [11]Etablissement Public de Santé Maison Blanche, Paris, France; [12]Université Clermont Auvergne, Clermont-Ferrand, France; [13]Department of Psychiatry, Early Psychosis Section, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [14]Department of Psychiatry, Icahn School of Medicine at Mount Sinai, NY; [15]Department of Medicine, Psychiatry Area, School of Medicine, Universidad de Oviedo, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Oviedo, Spain; [16]Barcelona Clinic Schizophrenia Unit, Neuroscience Institute, Hospital clinic, Department of Medicine, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain; [17]Department of Psychiatry, School of Medicine, Universidad de Valencia, Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Valencia, Spain; [18]Department of Psychiatry, Servicio de Psiquiatría Hospital "Virgen de la Luz", Cuenca, Spain; [19]Department of Psychiatry, Psychiatric Genetic Group, Instituto de Investigación Sanitaria de Santiago de Compostela, Complejo Hospitalario Universitario de Santiago de Compostela, Spain; [20]Division of Psychiatry, Department of Neuroscience and Behaviour, Ribeirão Preto Medical School, University of São Paulo, São Paulo, Brazil; [21]Department of Preventive Medicine, Faculdade de Medicina, Universidade of São Paulo, São Paulo, Brazil; [22]Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, South Limburg Mental Health Research and Teaching Network, Maastricht University Medical Centre, Maastricht, The Netherlands; [23]Vrije Universiteit Amsterdam, Department of Clinical, Neuro- and Developmental Psychology; [24]Department of Psychiatry, University of Cambridge, Cambridge, UK; [25]CAMEO Early Intervention Service, Cambridgeshire & Peterborough NHS Foundation Trust, Cambridge, UK; [26]Psylife Group, Division of Psychiatry, University College London, London, UK; [27]Section of Psychiatry, Department of Neuroscience, Biomedicine and Movement, University of Verona, Verona, Italy; [28]Section of Psychiatry, Azienda Ospedaliera Universitaria Integrata di Verona, Verona, Italy; [29]Division of Psychological Medicine and Clinical Neurosciences, MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK; [30]Department Psychiatry, Brain Centre Rudolf Magnus, Utrecht University Medical Centre, Utrecht, The Netherlands; [31]Centre for Genomic Sciences, Li KaShing Faculty of Medicine, The University of Hong Kong, Hong Kong, China; [32]Institute for Molecular Bioscience, University of Queensland, Australia

*To whom correspondence should be addressed; Department of Biomedicine, Neuroscience, and Advanced Diagnostics, University of Palermo, Via G. La Loggia 1, 90129 Palermo, Italy, tel: +39(0)916555641, e-mail: giada.tripoli@unipa.it

Background and Hypothesis: Facial Emotion Recognition is a key domain of social cognition associated with psychotic disorders as a candidate intermediate phenotype. In this study, we set out to investigate global and specific facial emotion recognition deficits in first-episode psychosis, and whether polygenic liability to psychotic disorders is associated with facial emotion recognition. *Study Design:* 828 First Episode Psychosis (FEP) patients and 1308

population-based controls completed assessments of the Degraded Facial Affect Recognition Task (DFAR) and a subsample of 524 FEP and 899 controls provided blood or saliva samples from which we extracted DNA, performed genotyping and computed polygenic risk scores for schizophrenia (SZ), bipolar disorder (BD), and major depressive disorder (MD). *Study Results:* A worse ability to globally recognize facial emotion expressions was found in patients compared with controls [$B = -1.5$ (0.6), 95% CI -2.7 to -0.3], with evidence for stronger effects on negative emotions (fear [$B = -3.3$ (1.1), 95% CI -5.3 to -1.2] and anger [$B = -2.3$ (1.1), 95% CI -4.6 to -0.1]) than on happiness [$B = 0.3$ (0.7), 95% CI -1 to 1.7]. Pooling all participants, and controlling for confounds including case/control status, facial anger recognition was associated significantly with Schizophrenia Polygenic Risk Score (SZ PRS) [$B = -3.5$ (1.7), 95% CI -6.9 to -0.2]. *Conclusions:* Psychosis is associated with impaired recognition of fear and anger, and higher SZ PRS is associated with worse facial anger recognition. Our findings provide evidence that facial emotion recognition of anger might play a role as an intermediate phenotype for psychosis.

Key words: facial affect recognition/genetic liability/first episode psychosis

Introduction

Psychotic disorders are polygenic syndromes, with many common genetic variants contributing to the risk of illness onset. The Psychiatric Genomic Consortium (PGC) identified 108 specific genetic loci reaching genome-wide significance for schizophrenia. These are common genetic variants that can be summarized into an individual polygenic risk score (PRS).[1-3] Before the GWAS era, studies on twins and first-degree relatives of patients suggested that the genes implicated in the risk of schizophrenia and related disorders affect some heritable traits on the causal pathway to the illness.[4] Those traits, known as intermediate phenotypes, are "simpler clues to genetic underpinnings than the disease syndrome itself,"[5] and putatively more directly influenced by risk genes.[6] Therefore, they might represent useful research targets to help unravel the biological mechanisms contributing to these disorders.

Patients with psychosis tend to show impairments in social cognition which refers to the set of psychological processes involved in the perception, encoding, storage, retrieval, and regulation of information about other people and self. Facial emotion recognition is a key domain of social cognition that has been extensively studied in schizophrenia and other psychotic disorders. Indeed, deficits in facial emotion recognition represent a well-replicated finding in schizophrenia,[7,8] detected at psychosis onset with the same severity as at more advanced stages of illness, especially for negative emotions.[9-11] Whether the deficits in psychosis concern recognition

of all emotions, or whether there is differential recognition ability across emotions, still requires further investigation, but increasing evidence, from meta-analysis[9] and from the largest studies to date,[11,12] suggests the most prominent deficits are in fear and/or anger.

Facial emotion recognition was reported to remain stable in psychosis over a 3-year follow-up period.[13,14] Furthermore, unaffected relatives of psychotic patients show intermediate performance compared with their affected relatives and controls,[15-18] supporting the hypothesis that emotion recognition might be a marker of liability for psychotic disorders. Emotion recognition has therefore been suggested as an intermediate phenotype which, as with other cognitive domains, was found to be polygenic.[19,20]

Studies testing the genetic association between psychotic disorders and facial emotion recognition ability have had mixed results. Germine et al[21] found an association between PRS for schizophrenia and social cognition—in particular, facial emotion identification efficiency – in two different samples, spanning from childhood to young adulthood; the findings suggest a potential role of emotion recognition in the genetic risk for schizophrenia. The study focused on emotion recognition in general and did not assess recognition of specific emotions. However, Xavier[22] found no association with general facial emotion recognition in ~700 patients with chronic schizophrenia testing SZ PRS, and Coleman et al[20] found that, after correction for 33 statistical tests, there were no significant associations between polygenic risk scores for mental disorders and facial emotion recognition ability (neither general nor specific) in a large population cohort of ~4000 children aged 8 years old. Although Coleman et al's negative study is the largest study to date (to our knowledge) to examine this topic, it is possible that genetic risk for schizophrenia only manifests in emotion recognition deficits after age 8. We, therefore, reasoned that examining, in a large sample, associations between PRS for schizophrenia and emotion recognition, could help resolve previous partly contradictory results. We also wanted to examine any relationship between genetic risk for schizophrenia and recognition of specific emotions. While our primary focus is on risk for schizophrenia, we also wanted to examine risk for other mental disorders (Bipolar disorder and depression) to help put any associations into context, acknowledging recent findings on shared genetic components among psychiatric disorders.[23]

In the current study, we report data concerning recognition of angry, fearful, happy, and neutral faces from the large multi-country European Network of national schizophrenia networks studying Gene-Environment Interactions (EUGEI) case-control study of first-episode psychosis. We aimed to confirm previous findings that FEP patients' exhibit lower facial recognition of fear and anger compared with controls, and we wished to take advantage of this well-powered study to investigate the

extent to which facial recognition deficits in psychosis extend to other emotions. We hypothesized that polygenic risk score for schizophrenia (SZ PRS), would be associated with lower emotion recognition ability, particularly as regards to fear and anger. In secondary analyses, we examined whether PRS for Bipolar Disorder and for Major Depression would be associated with emotion recognition deficits.

Materials and Methods

Design and Procedure

The EU-GEI study Work-Package 2 (WP2) employed a case-control design collecting data with an extensive battery of demographic, clinical, social, and biological measures (Core assessment); psychological measures, and cognitive tasks. EU-GEI WP2 participants with complete Degraded Facial Affect Recognition (DFAR) task and Benton Face Recognition Test (BFRT) data were included in the current study. All the researchers involved in administering the assessments undertook a training organized by a technical working committee of the overall EU-GEI study at the beginning and throughout the study. Inter-rater reliability (0.75) was assessed annually to warrant comparability of procedures and methods across sites.

Participants

Participants were recruited and assessed as part of the incidence and first episode case-control study, conducted as part of the EU-GEI programme.[24-26] The study was designed to investigate risk factors for psychotic disorders between May 1, 2010, and April 1, 2015, in 17 catchment areas in England, France, the Netherlands, Italy, Spain, and Brazil.

Patients were included if they met the following criteria during the recruitment period: (*a*) aged between 18 and 64 years; (*b*) presentation with a clinical diagnosis for an untreated FEP, even if longstanding (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] codes F20-F33); (*c*) resident within the catchment area at first presentation. Exclusion criteria were: (*a*) previous contact with psychiatric services for psychosis; (*b*) psychotic symptoms with any evidence of organic causation; and (*c*) transient psychotic symptoms resulting from acute intoxication (ICD-10: F1x.5).

Inclusion criteria for controls were: (a) aged between 18 and 64 years; (b) resident within a clearly defined catchment area corresponding to that of cases at the time of consent into the study; (c) sufficient command of the primary language at each site to complete assessments; and (d) no current or past psychotic disorder. To select a population-based sample of controls broadly representative of local populations in relation to age, sex, and ethnicity, a mixture of random and quota sampling was adopted. Quotas for control recruitment were based on the most accurate local demographic data available, and then filled using a variety of recruitment methods, including through (1) random sampling from lists of all postal addresses (e.g., in London); (2) stratified random sampling via General Practitioner (GP) lists (e.g., in London and Cambridge) from randomly selected surgeries; and (3) ad hoc approaches (e.g., internet and newspaper adverts, leaflets at local stations, shops, and job centers). All participants provided informed, written consent. Ethical approval was provided by relevant research ethics committees in each of the study sites. All data were stored anonymously.

Measures

Information about age, sex, and self-reported ethnicity was collected from cases and controls using the Medical Research Council (MRC) Sociodemographic Schedule.[27] Psychopathology was assessed using the OPerational CRITera system (OPCRIT).[28] Item response modeling was previously used to develop a bi-factor model composed of general and specific dimensions of psychotic symptoms (positive, negative, disorganization, mania, and depression).[29] The Community Assessment of Psychic Experience (CAPE) was used as a self-report measurement of lifetime psychotic experiences in controls with good reliability for all the languages spoken in the EUGEI catchment areas (http://www.cape42.homestead.com/). Previous factor analyses on the CAPE showed a three-factor structure of positive, negative, and depressive dimensions.[30] The short form of the Wechsler Adult Intelligence Scale (WAIS) III[31,32] was administered as an indicator of general cognitive ability (IQ). We used the Degraded Facial Affect Recognition (DFAR) task,[33] which has been used in numerous previous psychiatric research studies;[12-15,34-38] it assesses emotional face recognition in degraded photographs of four different actors (two females, and two males) representing four emotions: anger, fearful, happy, and neutral. Subjects were presented with 64 trials, and 16 presentations in each condition on a computer screen and asked to indicate the expression of each face by a button press (1 for angry, 2 for happy, 3 for fearful, and 4 for neutral). Variables generated by DFAR performance were the percentage of correctly recognized total facial expressions (DFAR total), neutral (DFAR neutral), happy (DFAR happy), fearful (DFAR fearful), and angry facial expressions (DFAR angry). The type of misinterpretation for each emotion was also computed. To account for general facial recognition ability, the short form (16 items) of the Benton Facial Recognition test (BFRT)[39] was administered to measure the ability to match non-emotional unfamiliar faces. We excluded the poorest performers by excluding participants who scored equal or below chance level ($\leq 25\%$) on DFAR total (FEP $N = 14$, controls $N = 17$), as they may not have engaged

with the task, and we covaried for BFRT to account for general facial recognition performance.

Polygenic Risk Scores

The case–control genotyped WP2 EUGEI sample (N = 2169; cases' samples N = 920, controls' samples N = 1248) included DNA extracted from blood (N = 1857) or saliva (N = 312). The samples were genotyped at the MRC Centre for Neuropsychiatric Genetics and Genomics in Cardiff (UK) using a custom Illumina HumanCoreExome-24 BeadChip genotyping array covering 570 038 genetic variants. For genotype Quality Control, we excluded SNPs with minor allele frequency <0.5%, Hardy Weinberg Equilibrium $P < 10^{-6}$, missingness >2%. For sample Quality Control, we excluded samples with >2% missing genotype, heterozygosity Fhet >0.14 or <−0.11, and those who presented genotype–phenotype sex mismatch or clustered with African ancestry in Principal Components Analysis (PCA) (N = 170). PCA was applied to genotype data to detect and correct our analysis for population stratification.[40] The final sample of 1720 individuals (1112 of European ancestry, 608 of any other ancestries but not black African) comprised 1041 controls and 679 patients. Imputation was performed through the Michigan Imputation Server, using the Haplotype Reference Consortium reference panel with the Eagle software for inferring haplotype phase, and Minimac3 for genotype imputation.[41-43] The imputed variants with r^2 <0.6, MAF <0.1% or missingness >1% were excluded.

The polygenic risk scores for schizophrenia, bipolar disorder, and major depression disorder were built using, as training data sets, the results from the last available mega-analyses from the Psychiatric Genomics Consortium (PGC).[3,44-47] In PRSice, individuals' number of risk alleles in the target sample was weighted by the log odds ratio from the discovery sample and summed into the PRSs at 0.05 SNPs Pt-thresholds (*a priori* selected). We excluded people of homogeneous African ancestry since in this population the SZ PRS from the PGC2 we calculated, as reported by other studies,[1,48] failed to explain a significant proportion of the variance (R^2 = 1.1%, P = .004).

Statistical Analysis

Analyses were conducted in STATA 15.[49] Preliminary descriptive analyses were performed using chi-square and t-tests to examine the differences in age, sex, ethnicity, IQ, BFRT, and DFAR scores between cases and controls. Linear mixed-effects models were built to estimate the relationship between overall and emotion-specific DFAR scores with case/control status, adjusted for age, sex, ethnicity, BFRT, and IQ as covariates, and country as a random effect. Those analyses were repeated with errors patterns for each condition as outcome variables (see supplement). Regression coefficients represent the strength of association between emotion recognition and case/control status; we inspected 83% confidence intervals[50] on these coefficients from separate regressions to examine whether the strength of association between emotion recognition and case-control status differed significantly for different emotions (reported in supplement). We also performed repeated measures mixed model analysis, examining emotion by case-control status interaction terms (see supplement). Associations between emotion recognition and symptom dimensions in cases and PLE in controls were examined using Pearson's correlation coefficient (reported in supplement). To investigate whether lower emotion recognition ability was associated with the liability for schizophrenia, bipolar, and major depression disorders, we considered SZ, BP, and MDD PRSs as predictors adjusting for case/control status, age, sex, BFRT, IQ, and 20 principal components (PCs) to control for population stratification in linear mixed-effects models with country as a random effect. Our primary interest in the PRS analysis was in examining relations between schizophrenia PRS and negative facial emotion recognition (fear and anger). Other PRS analyses were to provide context and are of secondary interest. Therefore, in consonance with Rothman,[51] corrections for multiple testing were not applied.

Results

Sample Characteristics

FEP patients and controls were included in the current study if data on both DFAR and BFRT were available. This led to a sample of 828 FEP patients and 1308 controls for the analysis.

Patients were younger (mean age = 30.9 ± 10.6 vs. 36.2 ± 13; t = 9.9, $P < .001$), with more men [61.8% (512) vs. 47.4% (620); $\chi^2(1)$ = 42.4, $P < .001$], and more frequently from minority ethnic backgrounds ($\chi^2(5)$ = 49.3, $P < .001$) compared with controls (table 1). The aforementioned differences are those expected when comparing psychotic patients with the general population.

Table 1 also shows that IQ scores were lower in cases compared with controls.

Facial Emotion Recognition and Psychosis

All DFAR scores and BFRT score were lower in patients compared with controls (tables 2 and 3). After adjusting for age, sex, ethnicity, BFRT score, and IQ, case-control status was still associated with worse ability to globally recognize facial emotion expressions [B = −1.5 (0.6), 95% CI −2.7 to −0.3; P = .013]. The specific emotions with the largest case control regression coefficients were fear [B = −3.3 (1.1), 95% CI −5.3 to −1.2; P = .002] and anger [B = −2.3 (1.1), 95% CI −4.6 to −0.1; P = .041]. Regression coefficients for case control status were significantly stronger for fear and anger expression recognition

Table 1. Demographic and cognitive characteristics of the sample included in the analysis

	Controls N=1308	FEP N=828	Df	Test Statistics	*P* value
Age (mean; sd)	36.2 (13)	30.9 (10.6)	2134	*t* = 9.9	<.001
Sex (male %; *N*)	47.4 (620)	61.8 (512)	1	χ^2 = 42.4	<.001
Ethnicity (%; *N*)					
White	77.4 (1012)	64.4 (533)	5	χ^2 = 49.3	<.001
Black	8.4 (110)	14.9 (123)			
Mixed	8.6 (112)	11.5 (95)			
Asian	2.3 (30)	2.9 (24)			
North African	1.7 (22)	4.2 (35)			
Other	1.7 (22)	2.2 (18)			
IQ (mean; SD)	102.7 (17.7)	85.6 (18.1)	2041	*t* = 20.9	<.001

IQ, intelligence quotient.

than for the happy facial expression recognition analysis (see for inspection of not overlapping 83% confidence interval, table S4 in supplement). Emotion by case–control status interaction analysis also indicated more prominent deficits in anger and fear recognition in psychosis (table S8a,b in supplement). The analysis on misattribution patterns (table S2 in supplement) highlighted that fearful expressions were mostly mistaken for neutral [*B* = 2.2, 95%

CI 0.2 to 4.2; *P* = .033] and happy emotions [*B* = 1.2, 95% CI 0.5 to 1.8; *P* = .001] by patients, whereas angry faces were incorrectly recognized as neutral [*B* = 1.8, 95% CI −0.03 to 3.5; *P* = .053].

Facial Emotion Recognition and PRSs for Schizophrenia, Bipolar Disorder, and Major Depression

The analysis on PRSs was performed in a subsample of 524 FEP and 899 population controls, controlling for case/control status and other covariates (see methods). Results are summarized in table 4 and illustrated in figure 1 for cases and figure 2 for controls separately.

SZ PRS was negatively associated with DFAR anger [*B* = −3.5 (1.7), 95% CI −6.9 to −0.2; *P* = .040], and the strength of the effect for anger was notably stronger than the strength of the effect for happiness (supplement table S5). PRS for Major Depression and Bipolar PRS was not significantly associated with facial emotion recognition (table 4; figures 1 and 2). When testing the association separately for cases and controls, SZ PRS prediction of DFAR angry held statistical significance in controls only [*B* = −5.7 (2.2), 95% CI −10 to −1.4; *P* = .009] (figure 2).

Exploratory Analyses by Country

Due to suggestions that emerged during the review process, we conducted exploratory analyses to probe differences between countries. Case-control deficits appeared (on inspection) especially prominent in Italy and Brazil (figure S3). We, therefore, repeated analyses, but now including country by case-control status as interaction terms. Results (supplementary table S9), indicated there were interactions between case-control status and country (driven by Italy and Brazil) for global DFAR and for anger recognition, but not fear recognition. This provides evidence that fear recognition deficit conclusions can be drawn from analyses without interaction terms, and so can be generalized across countries, but anger recognition deficits in psychosis appear to differ across countries. We also conducted a sensitivity analysis of
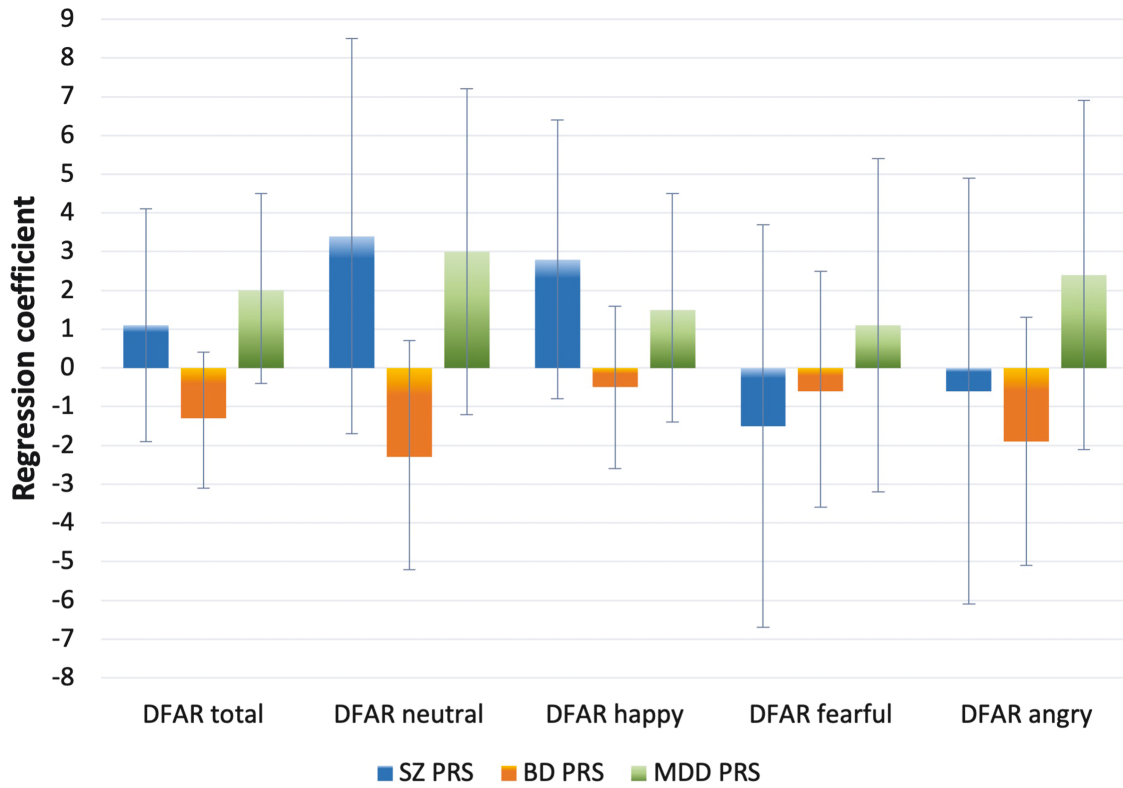
Table 2. DFAR and BFRT scores in FEP and controls

	Controls N = 1308	FEP N = 828	Df	Test statistics	*P* value
DFAR total	72.4 (12.1)	68.5 (13.6)	2134	*t* = 6.9	<.001
DFAR neutral	79.9 (17)	75.9 (21.9)	2134	*t* = 4.7	<.001
DFAR happy	87.8 (13.3)	86.2 (15.1)	2134	*t* = 2.6	.0095
DFAR fearful	55.2 (20.9)	50 (21.7)	2134	*t* = 5.5	<.001
DFAR angry	66.8 (22.3)	61.9 (23.1)	2134	*t* = 4.8	<.001
BFRT score	22.1 (2.2)	21.2 (2.8)	2134	*t* = 8.2	<.001

Table 3. DFAR scores' prediction by case/control status

Model	Case/control status			
	B	SE	95% CI	*P* value
DFAR total[a]	−3.2	0.6	−4.3 to −2.1	<.001
DFAR total[b]	−1.5	0.6	−2.7 to −0.3	.013
DFAR neutral[a]	−2.9	0.9	−4.6 to −1.2	.001
DFAR neutral[b]	−0.6	0.9	−2.4 to 1.2	.506
DFAR happy[a]	−0.9	0.6	−2.2 to 0.4	.160
DFAR happy[b]	0.3	0.7	−1 to 1.7	.639
DFAR fear[a]	−5.1	0.9	−6.9 to −3.1	<.001
DFAR fear[b]	−3.3	1.1	−5.3 to −1.2	.002
DFAR anger[a]	−3.9	1	−5.9 to −1.9	<.001
DFAR anger[b]	−2.3	1.1	−4.6 to −0.1	.041

Note: DFAR, degraded facial affect recognition.
[a]Adjusted for age, sex, ethnicity, BFRT score.
[b]Adjusted for age, sex, ethnicity, BFRT score, IQ. Models were random-intercept models that included one random effect to allow DFAR scores to vary across countries.

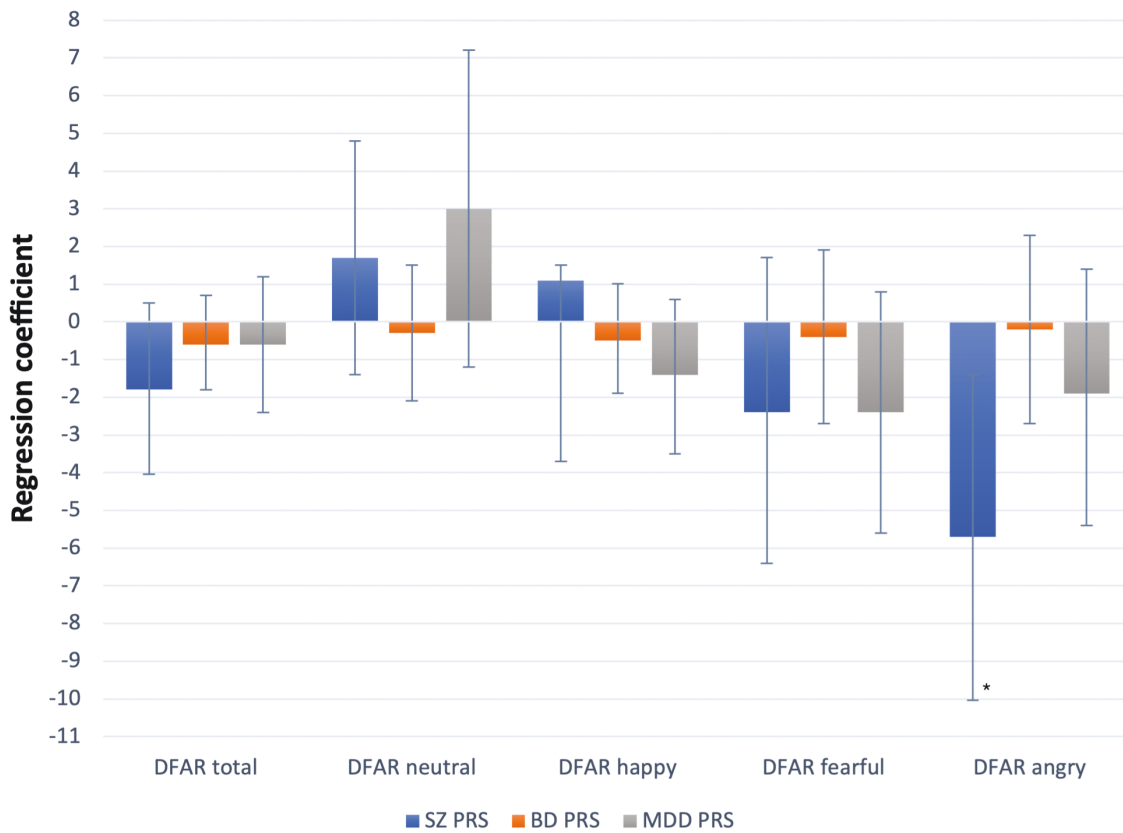**Fig. 1.** Associations between DFAR scores and SZ, BD, and MDD PRSs in FEP. Error bars indicate 95% CI.

Fig. 2. Associations between DFAR scores and SZ, BD, and MDD PRSs in controls. Error bars indicate 95% CI. *P = .009.

repeating some analyses having excluding participants from Italy and Brazil (table S10).

Discussion

The present study was conducted to investigate impairments in an important social cognition domain, facial emotion recognition, at first presentation for a psychotic disorder. For this purpose, we used the largest to date incidence sample of FEP patients and population-based controls. Moreover, we tested the association between global and specific emotion recognition and genetic susceptibility to schizophrenia and affective disorders.

As we expected, facial emotions were poorly recognized by patients compared with controls. This is in line with previous literature on patients at the first episode as well as with multi-episode and long-standing schizophrenia which reported a generalized deficit in emotion recognition.[9,10,12,13,52] In the same sample, we recently demonstrated that the patient group had deficits in probabilistic reasoning, yet these were no longer present after adjusting for IQ, and indeed were fully mediated by deficits in IQ.[53] Associations between emotion recognition and general cognitive abilities were previously reported in both childhood[54] and adulthood.[15] In our sample adjusting for IQ leads to a partial, but not complete, attenuation of the effect size (table 3), though the picture is more complex when probing differences between countries (see supplementary material). Facial emotion recognition difficulty in psychosis may be partially, but not entirely, related to general intellectual deficit and may in some circumstances be present even when general cognitive ability is preserved. We found that FEP patients had the most difficulty in recognizing fearful and angry faces, and were indeed statistically more impaired on these emotions than on happiness. This is broadly consistent with previous literature on early psychosis, but we go beyond prior studies as the current large sample size allows us to examine relative effect sizes with a degree of precision using confidence intervals. Barkl[9] examining specific emotions' identification accuracy in their meta-analysis, found that recognition of fear was the most consistent deficit across six studies. Catalan[13] and Caldiroli[12] reported a more prominent deficit of anger identification, in 64 FEP patients and 110 actively unwell FEP patients respectively, compared to controls. Fett,[38] employed a very large sample size ($n = 1032$ patients with nonaffective psychosis and $n = 579$ controls) and found patient deficits in anger and fear recognition but not in recognition of happy and neutral faces; however, they did not formally compare the effect sizes of group differences between emotions. Together, our data and prior studies indicate that fear and anger are the facial emotions with the most prominent deficits in psychosis. Moreover, the examination of error patterns made by our participants revealed that negative emotions were more mistaken for either neutral or happy by patients; this is in line with previous studies taking into account error patterns in FEP.[11,13] We did not find significant difficulties in recognizing neutral faces (after adjustment for IQ and other covariates), in contrast to some prior studies[13,55] nor was there any tendency to misattribute neutral and happy facial expressions for emotions with negative valence. Those results, along with either weak or no associations with any symptom dimensions (correlation coefficients ranging from –0.03 to 0.1, see supplement) or with psychotic-like experiences (correlation coefficients ranging from –0.01 to 0.1, see supplement), are consistent with the hypothesis of a specific impairment of recognizing negative emotions not strongly related to levels of symptomatology or salience misattribution,[15] but to social-emotional processing disturbances possibly preceding the onset of the disorder.[56]

The evidence from our case-control analysis for a specific emotion identification deficit in psychosis was partly corroborated in our study by the PRS analysis. Genetic liability to schizophrenia was associated with greater impairment in identifying angry emotional faces. We note that a previous study testing the association between schizophrenia polygenic risk score and facial emotion recognition by Xavier[22] on a sample of ~700 patients with chronic schizophrenia did not detect any association between SZ PRS and facial emotion identification, perhaps because of insufficient power or because there may be other factors in chronic patients that cloud the association such as current illness state;[12] similarly, in our study no association between SZ PRS and emotion

Table 4. DFAR scores' prediction by SZ PRS, BD PRS, and MDD PRS

Model	SZ PRS			
	B	SE	95% CI	*P* value
DFAR total	−0.7	0.9	−2.5 to 1.1	.466
DFAR neutral	2.6	1.4	−0.1 to 5.4	.060
DFAR happy	0.3	1.1	−1.8 to 2.4	.784
DFAR fear	−2.4	1.6	−5.6 to 0.8	.136
DFAR anger	−3.5	1.7	−6.9 to −0.2	.040
	BD PRS			
DFAR total	−0.6	0.5	−1.7 to 0.4	.220
DFAR neutral	−0.8	0.8	−2.4 to 0.7	.297
DFAR happy	−0.5	0.6	−1.8 to 0.7	.383
DFAR fear	−0.6	0.9	−2.4 to 1.2	.525
DFAR anger	−0.7	0.9	−2.7 to 1.2	.459
	MDD PRS			
DFAR total	0.2	0.7	−1.3 to 1.6	.793
DFAR neutral	2.7	1.1	0.5 to 4.9	.017
DFAR happy	−0.3	0.9	−1.9 to 1.4	.743
DFAR fear	−1.2	1.3	−3.8 to 1.3	.347

Note: Linear regression models adjusted for case/control status, age, sex, BFRT, IQ, and 20 PCs.
SZ, schizophrenia; BD, bipolar disorder; MDD, major depression disorder; PRS, polygenic risk score; DFAR, degraded facial affect recognition.

identification reached conventional statistical significance when we tested SZ PRS in patients only ($N = 524$). Whereas, the association between genetic risk for schizophrenia and worse anger recognition ability held in controls when analyzed separately, probably due to increased power ($N = 899$).

A PRS analysis is in some ways analogous to traditional familial risk studies in relatives of patients. Research conducted on siblings and first-degree relatives of patients suffering from psychotic disorders found deficits in recognizing negative emotions in facial expressions compared to controls[15,16,57-59] although to a lesser degree than patients, though we acknowledge that not all familial studies have shown significant sibling differences.[37] To help put the schizophrenia PRS result into context, we went on to examine the genetics underpinning bipolar and major depression disorders and the ability to identify facial emotional expressions, but there were no significant associations. There is strong evidence for deficits in facial emotion recognition in affective disorder.[10,18,60] However, our primary genomic interest was in the schizophrenia PRS analysis given that (1) the FEP sample has more nonaffective, schizophrenia spectrum psychosis than bipolar psychosis or depressive psychosis, and (2) prior findings indicate that schizophrenia PRS explains more variance in schizophrenia caseness than the other psychiatric PRSs do for their respective disorders.[61] We note that the affective disorder PRSs are less well developed compared to the schizophrenia PRS (because of factors relating to genetic architecture in the case of depression and smaller discovery GWAS sample size for bipolar disorder). Further work in larger sample sizes, using improved PRS in future, will be required to examine the specificity of the PRS associations across different disorders with different emotions.

Limitations and Strengths

There are limitations to our study. We assessed facial emotion recognition ability using a static task that does not provide temporally transient signals in stimuli as real-world perception.[62] As different tests will probe slightly different aspects of emotion recognition, it will be important to examine the consistency of results using different measures. Nonetheless, studies using more ecological dynamic task found no differences in terms of quality of impairment.[63,64] We acknowledge the possibility that the high accuracy rate for neutral and happy faces in both cases and controls might be more related to the psychometric property of the DFAR task rather than the absence of impairment. Future research may employ social cognition measures recommended by international research groups to improve replicability. While our sample size is very large for a case-control study of cognition, it is modest for genetic analyses. In addition, the multi-ethnic origin of our participants required further reduction of the sample size. Furthermore, in the PRS analyses, we

controlled for population stratification by adjusting for 20 PCs.[65] In accordance with Rothman,[52] we did not correct for multiple testing; p values and confidence intervals of all tests are fully reported in tables, as recommended, and should be cautiously interpreted.

Our study has several strengths. This is the largest study to date of social cognition in patients at the onset of their psychosis illness and population controls, and the large size permits us to examine relative emotional specificity. As a moderate involvement of general cognitive ability in emotion recognition was previously detected,[15,66] our study is strengthened by taking into account IQ and general face recognition ability. The multi-site sample from different centers across Europe and Brazil increases the generalizability of our results,[9,11] and provides some ability for a preliminary exploration of cultural differences. Cultural and country differences could be investigated further in future, ideally in larger samples, with a more fine-grained analysis of why emotion recognition abilities may differ between countries and how this interacts with illness.

Conclusions

Our results indicate a predominantly negative emotion facial recognition impairment in early psychosis, mainly involving fear and anger. Additionally, our findings provide further evidence to consider angry emotion recognition as an intermediate phenotype for psychosis, shedding light on specific emotion identification ability associated with common genetic risk variants for schizophrenia.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

Disclosure

M. Di Forti reports personal fees from Janssen, outside the submitted work. R.M. Murray reports personal fees from Janssen, Lundbeck, Sunovion, and Otsuka, outside of the submitted work. M. Bernardo reports grants and personal fees from Adamed, Janssen-Cilag, Otsuka,

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