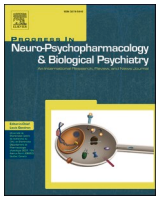
Progress in Neuropsychopharmacology & Biological Psychiatry 113 (2022) 110440

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

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



Examining facial emotion recognition as an intermediate phenotype for psychosis: Findings from the EUGEI study

Laura Fusar-Poli [a,1], Lotta-Katrin Pries [b,1], Jim van Os [b,c,d], Gamze Erzin [e], Philippe Delespaul [b,f], Gunter Kenis [b], Juryen J. Luykx [c,g,h], Bochao D. Lin [g], Alexander L. Richards [i], Berna Akdede [j], Tolga Binbay [j], Vesile Altınyazar [k], Berna Yalınçetin [l], Güvem Gümüş-Akay [m,n,o], Burçin Cihan [p], Haldun Soygür [q], Halis Ulaş [r,3], Eylem Şahin Cankurtaran [s], Semra Ulusoy Kaymak [t], Marina M. Mihaljevic [u,v], Sanja Andric-Petrovic [u,v], Tijana Mirjanic [w], Miguel Bernardo [x,y,z], Gisela Mezquida [x,y,z], Silvia Amoretti [x,y,z], Julio Bobes [z,aa,ab,ac], Pilar A. Saiz [z,aa,ab,ac], Maria Paz García-Portilla [z,aa,ab,ac], Julio Sanjuan [z,ad], Eduardo J. Aguilar [z,ad], José Luis Santos [z,ae], Estela Jiménez-López [z,af], Manuel Arrojo [ag], Angel Carracedo [ah,ai], Gonzalo López [z,aj], Javier González-Peñas [z,aj], Mara Parellada [z,aj], Nadja P. Maric [u,ak], Cem Atbaşoğlu [al], Alp Üçok [am], Köksal Alptekin [j,l], Meram Can Saka [al], Genetic Risk and Outcome of Psychosis (GROUP) investigators, Eugenio Aguglia [a], Celso Arango [z,aj], Michael O'Donovan [i], Bart P. F. Rutten [b,2], Sinan Guloksuz [b,an,*,2]

[a] Department of Clinical and Experimental Medicine, Psychiatry Unit, University of Catania, Catania, Italy
[b] Department of Psychiatry and Neuropsychology, School for Mental Health and Neuroscience, Maastricht University Medical Centre, Maastricht, the Netherlands
[c] Department of Psychiatry, UMC Utrecht Brain Centre, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands
[d] Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK
[e] Department of Psychiatry, University of Health Sciences Ankara Diskapi Training and Research Hospital, Ankara, Turkey
[f] FACT, Mondriaan Mental Health, Maastricht, Netherlands
[g] Department of Translational Neuroscience, UMC Utrecht Brain Center, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands
[h] GGNet Mental Health, Apeldoorn, the Netherlands
[i] MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, School of Medicine, Cardiff University, Cardiff, UK
[j] Department of Psychiatry, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey
[k] Department of Psychiatry, Faculty of Medicine, Adnan Menderes University, Aydin, Turkey
[l] Department of Neuroscience, Graduate School of Health Sciences, Dokuz Eylul University, Izmir, Turkey
[m] Department of Physiology, School of Medicine, Ankara University, Ankara, Turkey
[n] Brain Research Center, Ankara University, Ankara, Turkey
[o] Neuroscience and Neurotechnology Center of Excellence (NÖROM), Ankara, Turkey
[p] Department of Psychology, Middle East Technical University, Ankara, Turkey
[q] Turkish Federation of Schizophrenia Associations, Ankara, Turkey
[r] Department of Psychiatry, Faculty of Medicine, Dokuz Eylul University, Izmir, Turkey
[s] Güven Çayyolu Healthcare Campus, Ankara, Turkey
[t] Atatürk Research and Training Hospital Psychiatry Clinic, Ankara, Turkey
[u] Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[v] Clinic for Psychiatry Clinical Centre of Serbia, Belgrade, Serbia
[w] Special Hospital for Psychiatric Disorders Kovin, Kovin, Serbia
[x] Barcelona Clinic Schizophrenia Unit, Neuroscience Institute, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain
[y] Institut d'Investigacions Biomèdiques August Pi I Sunyer, Barcelona, Spain
[z] Biomedical Research Networking Centre in Mental Health (CIBERSAM), Spain
[aa] Department of Psychiatry, School of Medicine, University of Oviedo, Oviedo, Spain
[ab] Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain
[ac] Mental Health Services of Principado de Asturias, Oviedo, Spain
[ad] Department of Psychiatry, Hospital Clínico Universitario de Valencia, INCLIVA, School of Medicine, Universidad de Valencia, Valencia, Spain
[ae] Department of Psychiatry, Hospital Virgen de la Luz, Cuenca, Spain

* Corresponding author at: Maastricht University Medical Center, Vijverdalseweg 1, P.O.Box 616 6200 MD, Maastricht, the Netherlands.
E-mail address: sinan.guloksuz@maastrichtuniversity.nl (S. Guloksuz).

https://doi.org/10.1016/j.pnpbp.2021.110440
Received 29 July 2021; Received in revised form 12 September 2021; Accepted 12 September 2021
Available online 16 September 2021

[af] Universidad de Castilla-La Mancha, Health and Social Research Center, Cuenca, Spain
[ag] Department of Psychiatry, Instituto de Investigación Sanitaria, Complejo Hospitalario Universitario de Santiago de Compostela, Santiago de Compostela, Spain
[ah] Grupo de Medicina Genómica, Centro de Investigación Biomédica en Red de Enfermedades Raras (CIBERER), Universidad de Santiago de Compostela, Santiago de Compostela, Spain
[ai] Fundación Pública Galega de Medicina Xenómica (SERGAS), IDIS, Santiago de Compostela, Spain
[aj] Department of Child and Adolescent Psychiatry, Institute of Psychiatry and Mental Health, Hospital General Universitario Gregorio Marañón, IiSGM, School of Medicine, Universidad Complutense, Madrid, Spain
[ak] Institute of Mental Health, Belgrade, Serbia
[al] Department of Psychiatry, School of Medicine, Ankara University, Ankara, Turkey
[am] Department of Psychiatry, Faculty of Medicine, Istanbul University, Istanbul, Turkey
[an] Department of Psychiatry, Yale University School of Medicine, New Haven, CT, United States of America

ARTICLE INFO

Keywords:
Schizophrenia
Emotion
Social cognition
Schizotypal traits
Polygenic risk score

ABSTRACT

Background: Social cognition impairments, such as facial emotion recognition (FER), have been acknowledged since the earliest description of schizophrenia. Here, we tested FER as an intermediate phenotype for psychosis using two approaches that are indicators of genetic risk for schizophrenia: the proxy-genetic risk approach (family design) and the polygenic risk score for schizophrenia (PRS-SCZ).
Methods: The sample comprised 2039 individuals with schizophrenia, 2141 siblings, and 2049 healthy controls (HC). The Degraded Facial Affect Recognition Task (DFAR) was applied to measure the FER accuracy. Schizotypal traits in siblings and HC were assessed using the Structured Interview for Schizotypy-Revised (SIS-R). The PRS-SCZ was trained using the Psychiatric Genomics Consortium results. Regression models were applied to test the association of DFAR with psychosis risk, SIS-R, and PRS-SCZ.
Results: The DFAR-total scores were lower in individuals with schizophrenia than in siblings (RR = 0.97 [95% CI 0.97, 0.97]), who scored lower than HC (RR = 0.99 [95% CI 0.99–1.00]). The DFAR-total scores were negatively associated with SIS-R total scores in siblings (B = −2.04 [95% CI −3.72, −0.36]) and HC (B = −2.93 [95% CI −5.50, −0.36]). Different patterns of association were observed for individual emotions. No significant associations were found between DFAR scores and PRS-SCZ.
Conclusions: Our findings based on a proxy genetic risk approach suggest that FER deficits may represent an intermediate phenotype for schizophrenia. However, a significant association between FER and PRS-SCZ was not found. In the future, genetic mechanisms underlying FER phenotypes should be investigated trans-diagnostically.

1. Introduction

Cognitive impairments in people with psychotic disorders have been acknowledged since the earliest descriptions of these conditions (Bleuler, 1950). Both nonsocial and social cognition may be affected, with an impact on community functioning and quality of life (Green et al., 2019; Mucci et al., 2021; Velthorst et al., 2017). Nonsocial cognitive deficits have been under the lens of researchers for decades, but the literature on social cognitive function in psychoses has flourished mostly recently. Social cognition can be defined as a broad area that encompasses the mental operations needed to perceive, interpret, and process information for adaptive social interactions. Emotion processing, mentalizing, social perception, and attributional bias are components of social cognition (Green et al., 2019).

Emotion processing is frequently measured in schizophrenia research (Green et al., 2008). It can be defined as the ability to effectively identify emotions in others and to manage one's own emotions (Barrett and Salovey, 2002). Facial emotion recognition (FER) is particularly critical for effective social functioning and communication, as it involves the ability to evaluate emotions displayed in social situations (Green et al., 2019). There is substantial evidence confirming that FER is impaired in people with schizophrenia (Kohler et al., 2010), first-episode psychosis (Barkl et al., 2014), and individuals at risk for psychosis (van Donkersgoed et al., 2015).

It has been argued that FER deficits represent an intermediate phenotype for psychosis (Albacete et al., 2016; Andric et al., 2016; Leppänen et al., 2008; Li et al., 2010; Mendoza et al., 2011). The term "intermediate phenotype" indicates a trait that is in a predictable path from gene to behavior (Lenzenweger, 2013; Meyer-Lindenberg and Weinberger, 2006) This concept depends on the assumption that complex clinical phenotypes, such as psychiatric disorders, can be fragmented into several fundamental units. When the evaluation of complex clinical phenotypes may not provide enough mechanistic insights, the analysis of simpler and more biologically meaningful units (i.e. intermediate phenotypes) may help understand the causal pathways between genes and disorders. Eventually, this may facilitate the characterization of vulnerability factors (Blanco-Gómez et al., 2016; Flint et al., 2014).

Of note, the expression of an intermediate phenotype depends on the level of susceptibility to the complex clinical phenotype (Blanco-Gómez et al., 2016). FER appears to be associated with the severity of psychotic symptoms in schizophrenia (Maat et al., 2015) and with schizotypal dimensions among the non-psychotic population (Germine and Hooker, 2011; Morrison et al., 2013).

To investigate intermediate phenotypes, researchers previously applied different methodological approaches to capture genetic heritability, with one of the most prominent approaches being the family design (i.e. proxy genetic risk). In fact, intermediate phenotypes are observed in unaffected family members more often than in the general population (Leboyer et al., 1998). The proxy genetic risk approach relies on the premises that compared with the general population, unaffected first-degree relatives are more likely to share an enriched set of schizophrenia risk genes but do not manifest clinical symptoms. Recently, a large meta-analysis has confirmed that adult first-degree relatives of individuals with schizophrenia show moderate difficulties in FER compared to healthy controls (HC) (Martin et al., 2020).

The proxy-genetic risk approach provides valuable insight for the characterization of intermediate phenotypes. However, it does not provide insight into the specific molecular genetic variants associated with schizophrenia and the putative intermediate phenotype. Complementary methods such as polygenic risk scores (PRS) may help clarify the genetic substrate of FER deficits (Martin et al., 2020). PRS represent a single metric of molecular genetic risk and is estimated by summing

[1] Shared first authors.
[2] Shared last authors.
[3] Discharged by statutory decree No:701 at 8th July of 2018 because of signing "Peace Petition"

the log odds ratios of individual single nucleotide polymorphisms (SNPs) multiplied by the number of risk alleles present at the corresponding loci (Guloksuz et al., 2019; Wray et al., 2014). Studies have previously examined the association between FER and polygenic risk score for schizophrenia (PRS-SCZ) (Coleman et al., 2017; Germine et al., 2016; Xavier et al., 2018) of which only one specifically tested the association in a sample of individuals with psychosis (Xavier et al., 2018).

In the current study, we aim to test the hypothesis of FER as an intermediate phenotype for psychosis. By leveraging data from a large, multi-center, cross-European project, we—for the first time—applied two different but complementing approaches (i.e. proxy genetic risk and molecular genetic risk for schizophrenia) to estimate the genetic vulnerability in order to examine the path from social cognition to schizophrenia spectrum disorder. To triangulate evidence, we followed a three-step analytical plan. First, we tested the association between FER performance and proxy genetic risk for psychosis (i.e. schizophrenia, siblings, and HC) to examine differences in FER accuracy depending on the degree of genetic vulnerability to schizophrenia. Second, we examined the association between FER and schizotypal traits in siblings and HC to test the dimensional validity of the intermediate phenotype. Finally, we investigated the association between FER performance and genetic risk for schizophrenia by using molecular genetic risk for schizophrenia (PRS-SCZ).

2. Methods

2.1. Study participants

Data were derived from the Workpackage 6 (WP6) of the European Network of National Networks studying Gene-Environment Interactions in Schizophrenia (EUGEI) (European Network of National Networks studying Gene-Environment Interactions in Schizophrenia, 2014) and the Genetic Risk and Outcome for Psychosis (GROUP) studies, collected using uniform assessment schedules between 2010 and 2015 in the Netherlands, Turkey, Spain, and Serbia (Korver et al., 2012). EUGEI WP6 ("vulnerability and severity") was a cross-sectional study specifically conducted to investigate the role of gene-environment interaction of the vulnerability and severity of schizophrenia spectrum disorder and its intermediate phenotypes in a family-based setting. GROUP was a naturalistic longitudinal cohort study that started in 2004 in the Netherlands and Dutch-speaking part of Belgium and collected data at baseline, 3, and 6 years follow-ups over an approximate 10-year period.

Both projects were approved by the Medical Ethics Committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent and, in the case of minors, such a consent was also obtained from parents or legal guardians. Patients were diagnosed with schizophrenia spectrum disorders according to the DSM-IV-TR. Unrelated controls with no lifetime psychotic disorder were recruited from the same population as the cases. Exclusion criteria for all participants were a diagnosis of psychotic disorder due to another medical condition, a history of head injury with loss of consciousness, and an intelligence quotient (IQ) <70.

The current analyses used a merged dataset of GROUP baseline data and EUGEI WP6 cross-sectional data including 2039 cases, 2141 siblings, and 2049 unrelated HC.

2.2. Degraded Facial Affect Recognition Task (DFAR)

The Degraded Facial Affect Recognition Task (DFAR) was used as a measure of emotion recognition as the main outcome in line with previous studies (Meijer et al., 2012; Menghini-Müller et al., 2020; Modinos et al., 2020; Tognin et al., 2020; van't Wout et al., 2007; van't Wout et al., 2004). This performance-based social cognition task measures emotional face recognition in degraded photographs. Subjects were presented with photographs of four individuals (two males and two females), depicting emotional facial expression. Subjects were asked to indicate the expression of each face and to respond as accurately as possible. The photographs of the faces were passed through a filter resulting in a reduced visual contrast by 30%. This method was adopted to increase the difficulty and enhance the contribution of perceptual expectancies and interpretation. Subjects were presented with 64 trials (16 for each condition: angry, happy, fearful and neutral) (van't Wout et al., 2004). The percentage of total correct answers (DFAR-total) was the primary outcome of interest. Exploratory analyses were conducted on the percentages of correct answers per emotion domain (DFAR-neutral, −happy, −fearful, and -angry). Higher scores indicate a better ability to recognize facial expressions of a particular emotion. As DFAR was our primary outcome, participants with missing data on DFAR-total scores and subscales ($n = 579$) or unreliable data ($n = 18$) were excluded from the analyses. DFAR-total and subscales were correlated. The correlation matrix was reported in Table S1.

2.3. Diagnosis of schizophrenia spectrum disorder

Patients were diagnosed with schizophrenia spectrum disorders according to the DSM-IV-TR. Diagnoses were confirmed by the Operational Criteria Checklist for Psychotic and Affective Illness (McGuffin et al., 1991) in the EUGEI WP6, and by the Schedules for Clinical Assessment in Neuropsychiatry (Wing et al., 1990) and the Comprehensive Assessment of Symptoms and History (Andreasen et al., 1992) in the GROUP.

2.4. Schizotypal traits

In both GROUP and EUGEI, the Structured Interview for Schizotypy-Revised (SIS-R) was administered to siblings and HC. The SIS-R is a semi-structured interview containing 20 schizotypal symptoms and 11 schizotypal signs rated on a four-point scale (Kendler et al., 1989; Vollema and Ormel, 2000) to evaluate psychosis expression in the general population. Symptoms are defined as verbal responses to standardized questions concerning, for example, magical ideation, illusions, and referential thinking. Signs refer to behaviors that are rated by the interviewer such as goal-directedness of thinking and flatness of affect. Questions and rating procedures are standardized. Guided by previous research, 31 item scores were reduced a priori to two-dimensional scores representing the means of seven positive schizotypy items (i.e. SIS-R positive, covering the areas of referential thinking, psychotic phenomena, derealization, magical ideation, illusions, and suspiciousness) and eight negative/disorganized schizotypy items (i.e. SIS-R negative, covering the areas of social isolation, sensitivity, introversion, restricted affect, disturbances in associative and goal-directed thinking, poverty of speech, and eccentric behavior) (Pries et al., 2020; van Os et al., 2020).

2.5. Polygenic risk score for schizophrenia (PRS-SCZ)

Samples were genotyped at Cardiff University Institute of Psychological Medicine and Clinical Neurology, using a custom Illumina HumanCoreExome-24 BeadChip genotyping arrays containing probes for 570,038 genetic variants (Illumina, San Diego, CA). Genotype data were called using the Genome Studio package and transferred into PLINK format for further analysis. Quality control was conducted in PLINK v1.07 (Purcell et al., 2007) or with custom Perl scripts. Variants with a call rate < 98% were excluded from the data set. Hardy–Weinberg equilibrium *p*-value was calculated separately in Turkish, Northern European, and Southern European samples. Variants with Hardy–Weinberg equilibrium p-value $< 1 \times 10^{-6}$ in any of these three regions were excluded from the data set. After quality control, 559,505 variants remained.

Samples with a call rate < 98% were excluded from the dataset. A linkage disequilibrium pruned set of variants was calculated using the –indep-pairwise command in PLINK (maximum $r^2 = 0.25$, window size = 500 single nucleotide polymorphisms (SNPs), window step size = 50

SNPs) and used for further analyses. Homozygosity F values were calculated using the –het command in PLINK, and outlier samples ($F < -0.11$ or $F > 0.15$) were excluded. The genotypic sex of samples was calculated from X chromosome data using the check-sex command in PLINK, and samples with different genotypic sex to their database sex were excluded.

Identity-by-descent (IBD) values were calculated for the sample in PLINK. We excluded samples with siblings in the dataset according to the database record, but no siblings found by IBD analysis of the genotype data. Sibling status was defined as PI-HAT > 0.35 and < 0.65 in the IBD analysis. After these were removed from consideration, samples with two or more siblings in the database that were not supported by the genotypic data were also excluded.

After visually observing the clustering of errors by genotyping chips, we decided to exclude chips with a high proportion of errors. All samples on chips with five or more sample exclusions due to heterozygosity or call rate (out of 12 possible samples) were excluded. All samples on chips with four or more sample exclusions due to sex or relative checks were also excluded, unless their identity was corroborated by concordance between database and genotype relatedness data with a sample on another chip.

Genetic ancestry principal components (PCs) were calculated in PLINK using linkage disequilibrium (LD) pruned variants after combining the data set with the Thousand Genomes reference dataset. Due to the inherently multi-population nature of the dataset and the variety of possible analyses, no exclusions were made to the whole dataset based on this analysis. Population effects were corrected for separately in individual analyses. After quality control, genotypes were imputed on the Michigan Imputation Server using the Haplotype Reference Consortium reference panel (version 1.1) and the programs Eagle for haplotype phasing and Minimac3 for imputation (Das et al., 2016; Loh et al., 2016). After imputation, variants with an imputation $r^2 > 0.6$, minor allele frequency (MAF) $> 0.1\%$ and call rate $> 99\%$ were retained (8,277,535 variants). Best-guess genotypes were generated from genotype probabilities using PLINK.

PRS-SCZ was constructed using summary statistics from the second wave of the Psychiatric Genomics Consortium genome-wide association study (GWAS), excluding samples present in the GROUP data (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Clumping was performed in imputed best-guess genotypes for each data set using PLINK (maximum $r^2 = 0.2$, window size = 500 kb, minimum MAF = 10%, minimum INFO score = 0.7), and variants within regions of long-range LD around the genome (including the major histocompatibility complex) were excluded (Price et al., 2008). PRS-SCZ were then constructed from best-guess genotypes using PLINK at 10 different p-value thresholds (PT = 1, 0.5, 0.3, 0.2, 0.1, 0.05, 0.01, 1×10^{-4}, 1×10^{-6}, 5×10^{-8}). Consistent with previous research in the field (Sørensen et al., 2018) and previous work in this dataset (Pries et al., 2020; van Os et al., 2020), we used $p = 0.05$ for our primary analysis, as this threshold optimally captures liability to the disorder in the Psychiatric Genomics Consortium analysis (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

2.6. Statistical analysis

Stata software version 16.0 was used for the analysis (StataCorp, 2019). The nominal significance threshold was set to $P = 0.05$. First, the association between FER and status was tested using multinomial logistic regression analyses, with the status (i.e. case, unaffected sibling, or HC) as the dependent variable and each DFAR score (total, neutral, happy, fearful, and angry) as the independent variable. Effect sizes were expressed as relative risk ratio (RR) with their 95% confidence intervals. Second, the association between FER and schizotypal traits in unaffected siblings and HC was tested using linear regressions with DFAR categories as dependent variables and SIS-R scales as independent variables. Due to missing values of SIS-R (Table S2), this analysis was conducted using both multiple imputed SIS-R data and raw data. Under the assumption of missing at random, the multiple imputation chained equation (Royston and White, 2011) was applied with 20 imputations restricted to in-range values (relative efficiency $\geqslant 99\%$). Percentages of missing scores were reported in Table S2. Finally, in the subsample with genomic data available ($n = 4552$), the association between FER and PRS-SCZ was tested using multiple linear regressions with DFAR categories as dependent variables and PRS-SCZ as independent variable. As PRS-SCZ is accurate in European ancestry only (Burkhard et al., 2021), 413 participants with non-European ancestry were excluded from the genetic analysis (193 patients, 167 siblings, and 53 HC). All analyses including PRS-SCZ were also adjusted for ancestry using ten PCs. Age, sex, and country were included as covariates in all regression models that also took into account of clustering of observations within families, using the Stata "cluster" option. In line with previous research (Meijer et al., 2012), we did not adjust for IQ. As proposed by Rothman (Rothman, 1990), corrections for multiple testing were not applied for explorative analyses involving DFAR subscales.

3. Results

3.1. Characteristics of the sample

General characteristics of the sample and mean scores of DFAR and SIS-R are reported in Table 1.

3.2. Association between DFAR scores and psychosis risk

Multinomial logistic regressions showed a significant association between DFAR-total scores and psychosis risk. Compared to HC, both sibling status (RR = 0.99 [95% CI 0.99, 1.00]) and case status (RR = 0.96 [95% CI 0.96, 0.97]) were associated with lower DFAR-total scores. Case status was associated with lower DFAR-total scores than sibling status (RR = 0.97 [95% CI 0.97, 0.97]). Similar patterns of associations were seen for DFAR-neutral and DFAR-fearful scores, but not for DFAR-happy and angry (Table 2).

For DFAR-happy, cases scored lower than both HC (RR = 0.99 [95% CI = 0.99, 1.00]) and siblings (RR = 0.99 [95% CI 0.98, 0.99]), who scored higher than HC (RR = 1.01 [95% CI 1.00, 1.01]). DFAR-angry scores showed no significant differences between siblings and HC (RR = 1.00 [95% CI 1.00, 1.00]). Conversely, case status was associated with lower DFAR-angry scores than both HC (RR = 0.99 [95% CI 0.98, 0.99]) and siblings (RR = 0.99 [95% CI 0.98, 0.99]).

3.3. Association between DFAR scores and SIS-R dimensions in siblings and healthy controls

Analyses using raw data showed that DFAR-total scores were negatively associated with SIS-R total scores in both siblings (B = −2.04 [95% CI -3.72; −0.36]) and HC (B = −2.93 [95% CI -5.50, −0.36]) (Table 3). A negative association was also found between DFAR-total scores and SIS-R negative dimension in siblings (B = −2.20 [95% CI = −3.95, −0.45]) and HC (B = -3.54 [95% CI -6.29, −0.78]). No significant associations were found between DFAR-total score and SIS-R positive dimension (Table 3). Fig. 1 shows unadjusted linear prediction lines of DFAR-total on SIS-R dimensions per group.

DFAR-neutral scores showed different patterns of association in siblings and HC. In siblings, they were associated with SIS-R total (B = −3.74 [95% CI = −6.33, −1.14]) and negative dimension (B = −4.58 [95% CI = −7.38, −1.78]). In HC, there was an association with the SIS-R positive dimension only (B = −3.26 [95% CI = −6.01, −0.50]). DFAR-angry scores were associated with the negative dimension in HC only (B = −7.33 [95% CI = −11.84, −2.82]). DFAR-fearful scores showed no significant associations with SIS-R scores in siblings. In HC, DFAR-fearful scores were associated with SIS-R total (B = −5.90 [95% CI = −9.64, −2.16]), positive (B = −3.45 [95% CI = −6.20, −0.70]), and

Table 1
Characteristics of the sample ($N = 6229$).

	Cases ($n = 2039$)	Siblings ($n = 2141$)	Healthy controls ($n = 2049$)	Total (N = 6229)
Age, *M* (SD)	30.56 (8.77)	31.12 (9.45)	32.96 (10.58)	31.54 (9.68)
Sex, male n (%)	1454 (71.31)	965 (45.07)	1016 (49.59)	3435 (55.15)
Country, n (%)				
Turkey	587 (28.79)	619 (28.91)	1029 (50.22)	2235 (35.88)
Spain	410 (20.11)	494 (23.07)	428 (20.89)	1332 (21.38)
Serbia	52 (2.55)	54 (2.52)	46 (2.24)	152 (2.44)
Netherlands	990 (48.55)	974 (45.49)	546 (26.65)	2510 (40.30)
Education, n (%)				
No qualifications	175 (8.85)	103 (4.92)	42 (2.09)	320 (5.26)
With qualifications	523 (26.45)	379 (18.11)	383 (19.05)	1285 (21.13)
Tertiary	513 (25.95)	400 (19.11)	431 (21.44)	1344 (22.11)
Vocational	549 (27.77)	688 (32.87)	638 (31.74)	1875 (30.84)
University	217 (10.98)	523 (24.99)	516 (25.67)	1256 (20.66)
DFAR-total, *M* (SD)	66.42 (13.71)	72.43 (11.82)	73.91 (15.86)	70.95 (14.23)
DFAR-neutral, *M* (SD)	71.82 (23.13)	77.84 (18.51)	79.40 (20.67)	76.38 (21.07)
DFAR-happy, *M* (SD)	85.18 (16.47)	88.36 (13.50)	87.33 (17.56)	86.98 (15.95)
DFAR-angry, *M* (SD)	62.05 (22.24)	69.41 (20.65)	70.29 (23.50)	67.29 (22.44)
DFAR-fearful, *M* (SD)	46.84 (21.46)	54.37 (20.53)	58.88 (21.87)	53.39 (21.84)
SIS-R total, *M* (SD)	–	0.38 (0.33)	0.24 (0.24)	0.31 (0.29)
SIS-R positive, *M* (SD)	–	0.40 (0.42)	0.25 (0.32)	0.32 (0.38)
SIS-R negative, *M* (SD)	–	0.36 (0.34)	0.23 (0.23)	0.30 (0.30)

DFAR: Degraded Facial Affect Recognition Task, HC: healthy controls, SD: standard deviation; SIS-R: Structured Interview for Schizotypy-Revised.

negative dimensions (B = −5.73 [95% CI = −9.65, −1.81]) (Table 3). The results from the multiple imputed data were consistent (Table S3). Unadjusted linear prediction lines with 95% confidence interval of DFAR-neutral, happy, fearful, and angry subdomains on SIS-R dimensions per group are reported in Fig. S1.

3.4. Association between DFAR scores and polygenic risk score for schizophrenia (PRS-SCZ) in cases, siblings and healthy controls

No significant associations were found between DFAR scores and PRS-SCZ in cases, siblings, or HC (Table 4).

4. Discussion

The present study used the proxy-genetic risk approach (family design) and the PRS-SCZ to test whether FER represented an intermediate phenotype for psychosis in a large cross-European sample. In line with previous findings, the FER accuracy was lower in people with schizophrenia than HC (Fett et al., 2013; Kohler et al., 2010; Maat et al., 2015; Meijer et al., 2012). The differences between groups were significant but fairly modest. Moreover, the expression of "soft" phenotype (i.e. schizotypy) was associated with FER in siblings, as well as in HC. Overall, these findings suggest that FER impairments may manifest in relatives of individuals with schizophrenia, albeit to a minor degree. Although our findings using proxy genetic liability provided support for the heritability of FER deficits, there was no significant association between molecular genetic liability for schizophrenia (PRS-SCZ) and DFAR scores in either individuals with schizophrenia, siblings or HC.

Previous research proposed that FER deficits might be correlated with the symptom severity in schizophrenia (Fett et al., 2013; Maat et al., 2015). Our study showed similar patterns in siblings and HC, with higher total schizotypal symptoms being associated with lower FER accuracy, thereby lending further support to the psychosis continuum model across the general population (Guloksuz and van Os, 2017; van Os and Reininghaus, 2016). Interestingly, the association was significant for negative but not for positive schizotypal traits, similar to the findings reported in clinical samples (Ventura et al., 2013). A possible explanation is that the reduced capacity to experience (i.e. anhedonia) or express emotions (i.e. affective flattening) might be linked to the onset and the maintenance of social cognition impairments, including the ability of inferring others' emotions (Ventura et al., 2013).

We found no nominally statistically significant association between PRS-SCZ and DFAR scores. Our findings are in line with previous studies of emotion recognition showing no association between PRS-SCZ and DFAR (Coleman et al., 2017; Germine et al., 2016; Xavier et al., 2018). Interestingly, although Germine et al. (2016) did not find a significant association of PRS-SCZ with emotion recognition per se in a mixed sample of children and adults, an association was found for the speed of emotion identification (Germine et al., 2016). Therefore, the lack of association in our sample may be related to the fact that we measured the ability but not the speed of identifying emotions, which could be an intriguing target for future research.

Furthermore, there is a discrepancy between the results from the proxy-genetic risk approach and PRS-SCZ analyses. There may be

Table 2
Associations between DFAR scores and status (i.e., case, sibling, healthy control). Regressions models were adjusted for age, sex, country, and took into account of clustering of observations within families.

	Cases vs HC			Siblings vs HC			Cases vs siblings		
	RR	95% CI	P	RR	95% CI	P	RR	95% CI	P
DFAR-total	0.96	0.96, 0.97	<0.001*	0.99	0.99, 1.00	0.01*	0.97	0.97, 0.97	<0.001*
Subdomains									
DFAR-neutral	0.98	0.98, 0.98	<0.001*	0.99	0.99, 1.00	<0.001*	0.99	0.98, 0.99	<0.001*
DFAR-happy	0.99	0.99, 1.00	<0.001*	1.01	1.00, 1.01	0.008*	0.99	0.98, 0.99	<0.001*
DFAR-angry	0.99	0.98, 0.99	<0.001*	1.00	1.00, 1.00	0.73	0.99	0.98, 0.99	<0.001*
DFAR-fearful	0.98	0.97, 0.98	<0.001*	0.99	0.99, 0.99	<0.001*	0.98	0.98, 0.99	<0.001*

CI: Confidence interval, DFAR: Degraded Facial Affect Recognition Task, HC: healthy controls, RR: relative risk ratio,
* $P < 0.05$.

Table 3
Association between DFAR and SIS-R scores in siblings and healthy controls. Regressions models were adjusted for age, sex, country, and took into account of clustering of observations within families.

		Emotion recognition			Subdomains										
		DFAR-total			DFAR-neutral			DFAR-happy			DFAR-angry			DFAR-fearful		
		B	95% CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P
SIS-R total	Siblings	−2.04	−3.72, −0.36	0.02*	−3.74	−6.33, −1.14	0.005*	−1.12	−3.06, 0.82	0.26	−2.59	−5.45, 0.26	0.07	−0.56	−3.45, 2.33	0.70
	HC	−2.93	−5.50, −0.36	0.02*	−3.71	−7.57, 0.15	0.06	1.23	−1.81, 4.28	0.43	−3.27	−7.55, 1.00	0.13	−5.90	−9.64, −2.16	0.002*
SIS-R positive	Siblings	−1.07	−2.29, 0.14	0.08	−1.43	−3.33, 0.47	0.14	−0.44	−1.91, 1.03	0.56	−1.92	−4.03, 0.20	0.07	−0.42	−2.53, 1.69	0.69
	HC	−1.25	−3.11, 0.60	0.19	−3.26	−6.01, −0.50	0.02*	1.02	−1.22, 3.26	0.37	0.80	−2.36, 3.96	0.62	−3.45	−6.20, −0.70	0.01*
SIS-R negative	Siblings	−2.20	−3.95, −0.45	0.01*	−4.58	−7.38, −1.78	0.001*	−1.54	−3.52, 0.44	0.13	−2.27	−5.04, 0.50	0.11	−0.27	−3.18, 2.64	0.85
	HC	−3.54	−6.29, −0.78	0.01*	−2.04	−6.10, 2.02	0.32	0.92	−2.26, 4.09	0.57	−7.33	−11.84, − 2.82	0.001*	−5.73	−9.65, −1.81	0.004*

CI: Confidence interval, DFAR: Degraded Facial Affect Recognition Task, HC: healthy controls, SIS-R: Structured Interview for Schizotypy-Revised,
* $P < 0.05$.

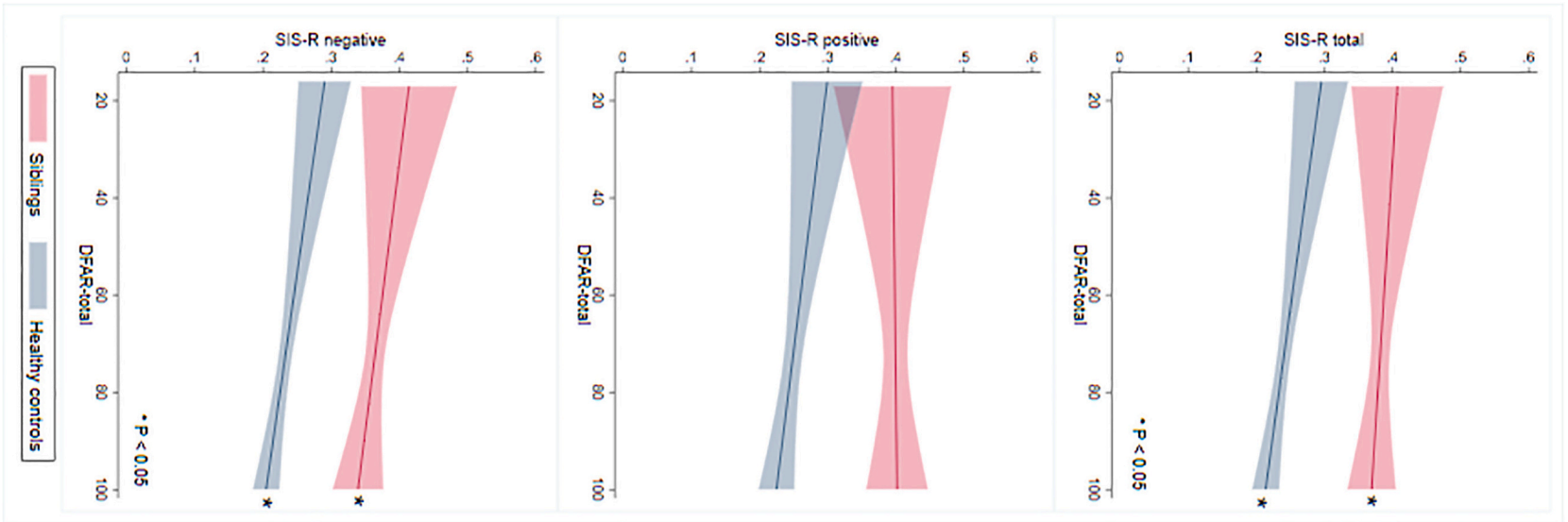


Fig. 1. shows unadjusted linear prediction lines with 95% confidence intervals of the Degraded Faces Affect Recognition task (DFAR) total scores on the domains of the Structured Interview for Schizotypy-Revised (SIS-R) in siblings and healthy controls.

Table 4
Association between DFAR scores and PRS-SCZ. Analyses were conducted in a subset of cases ($n = 1428$), siblings ($n = 1619$), and healthy controls ($n = 1505$) with European ancestry. Analyses were adjusted for age, sex, country, 10 principal components, and took into account of clustering of observations within families.

	Emotion recognition			Subdomains											
	DFAR-total			DFAR-neutral			DFAR-happy			DFAR-angry			DFAR-fearful		
	B	95% CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P	B	95% CI	P
Cases	−0.05	−0.36, 0.26	0.74	−0.07	−0.59, 0.45	0.78	0.05	−0.31, 0.42	0.77	−0.19	−0.68, 0.29	0.44	0.002	−0.49, 0.49	0.99
Siblings	0.09	−0.18, 0.36	0.49	0.05	−0.35, 0.45	0.81	0.22	−0.08, 0.53	0.15	0.02	−0.43, 0.47	0.92	0.08	−0.35, 0.51	0.71
HC	0.10	−0.29, 0.49	0.61	−0.05	−0.54, 0.45	0.85	0.11	−0.32, 0.54	0.61	0.24	−0.29, 0.77	0.37	0.11	−0.37, 0.60	0.65

CI: Confidence interval, DFAR: Degraded Facial Affect Recognition Task, HC: healthy controls, PRS-SCZ: polygenic risk score for schizophrenia.

several explanations underlying the supposedly discrepant findings. PRS-SCZ might not capture the specific genetic risk associated with the tested pathway from social cognition to schizophrenia spectrum disorders. For instance, a recent study found that cognition (a transdiagnostic phenotype) in individuals with schizophrenia was more strongly associated with PRSs that index cognitive traits in the general population than PRSs for neuropsychiatric disorders including schizophrenia (Richards et al., 2020). These findings suggest that genetic mechanisms underlying cognitive variation within schizophrenia may be at least partly independent from those that predispose an individual to schizophrenia diagnosis itself (PRS-SCZ). Therefore, although PRS-SCZ shows the most potential for developing PRS-based genomic prediction, it appears that the ideal approach would be to use PRS that is specifically constructed to capture genetic vulnerability for the putative intermediate phenotype, which is social cognition in this case. However, PRS for social cognition does not yet exist. The limitations of the narrow scope of GWAS that have principally focused on genetic vulnerability for individual diagnostic entities (e.g. schizophrenia, autism spectrum disorder [ASD], ADHD) rather than trans-diagnostic phenotypes have been discussed (Glahn and McIntosh, 2017). To overcome these limitations of PRSs in the future, a team of researchers in Psychiatric Genomics Consortium Schizophrenia Working Group is tasked with harmonizing phenotypical data that go beyond diagnosis. Hopefully, these efforts into enrichening phenotypes would result in more precise capturing of genetic architecture of putative transdiagnostic mechanisms and provide us with alternatives better than PRS-SCZ to put the intermediate phenotype theories to the test.

In this respect, the proxy-genetic risk approach, although a coarse measure, captures genetic vulnerability that is not captured by PRS-SCZ and may provide important evidence for putative intermediate phenotypes (Flint et al., 2014). Compared to heritability of around 80% estimated in twin-design studies, PRS-SCZ only explains 7.7% of the variance in liability attributable to schizophrenia, with the SNP-based heritability being around 24% (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2020). In addition to environment, missing heritability might be due to genetic markers and mechanisms that are not captured by the PRS-SCZ, which, however, are part of the heritability estimated by family studies. PRS-SCZ is estimated based on common variants; however, rare variants and rare structural changes confer risk for these highly complex mental disorder phenotype (Glahn and McIntosh, 2017). Indeed, they might have particular relevance for trans-diagnostically expressed social cognition impairments including FER deficits given its close connection with ASD, which is much more strongly associated with rare de novo mutations than with common variants (Glahn and McIntosh, 2017).

Our explorative analyses focused on the recognition of specific emotions. The analyses of neutral and fearful emotions yielded findings similar to those observed with total DFAR scores. Siblings and HC did not score differently in angry emotion, whereas happy emotions showed a different pattern: siblings were more accurate than cases and HC. These findings differ from a recent meta-analysis (Martin et al., 2020) that reported no differences in recognizing happy or neutral faces and worse performances in recognizing anger and fear in first-degree relatives of individuals with schizophrenia compared to HC. Nevertheless, these meta-analytical estimates were based on a small number of studies (six study for happy emotions, two for neutral, and eight for anger and fear) (Martin et al., 2020). Future studies may help clarify whether specific types of emotions, such as those with positive (happy) and negative valence (e.g., anger, fear, disgust), are differently identified by groups at high genetic risk for schizophrenia.

Our study is relevant both for researchers and clinicians. The research design of our study falls within the NIMH research priority, the Research Domain Criteria (RDoC) framework, prioritizing shared dimensional psychological constructs (e.g. social cognition) cutting across traditional diagnostic categories (Insel et al., 2010). Our findings may steer researchers toward investigating cross-diagnostic genetic mechanisms of FER deficits shared across several psychiatric disorders (Cotter et al., 2018). The identification of FER as a heritable trait linked to clinical phenotypes such as schizophrenia may help identify populations at risk and better understand underlying mechnanisms of emotion processing to develop specific treatment strategies.

To our knowledge, this is the largest study to test FER using a proxy-genetic risk approach and the first to evaluate its association using molecular genetic liability to schizophrenia in a sample stratified according to genetic risk. However, findings should be interpreted in light of some limitations. First, the cross-sectional design does not allow for drawing any causal inference. Nevertheless, our findings may lay the groundwork for longitudinal studies to explore the interplay between genetic risk, environmental exposures, and psychopathology in the context of emotion processing in schizophrenia. Second, we examined a single domain of social cognition: FER. In the future, other components of social cognition should be investigated to clarify whether the broad spectrum of socio-cognitive deficits might similarly represent an intermediate phenotype for psychosis. Third, although participants with IQ < 70 and a history of head injury with loss of consciousness that might affect FER were excluded, the presence of other psychiatric disorders, such as borderline personality disorder (Catalan et al., 2016; Mitchell et al., 2014) and depression (Bourke et al., 2010) was not evaluated and therefore might have an impact on FER responses. Additionally, to increase replicability, future research may employ tools for measuring social cognition that are proposed by international consortia (Carter et al., 2009; Green et al., 2005). Finally, our sample size was substantial, but it might be considered relatively small for a molecular genetic study. Therefore, we cannot disregard the fact that a lack of statistical power might have prevented us from detecting weaker associations between PRS-SCZ and FER in the stratified analyses.

5. Conclusion

Our findings are consistent with the hypothesis that FER might represent an intermediate phenotype for psychosis. Pre-registered confirmatory research in large genotyped samples and twin populations is required to replicate these findings and further investigate the molecular genetic mechanisms underlying this intermediate phenotype.

Financial support

The EUGEI project was supported by the European Community's Seventh Framework Program under grant agreement No. HEALTH-F2-2009-241909 (Project EU-GEI). Dr. Pries is supported by the Kootstra Talent Fellowship of Maastricht University. Dr. Erzin is supported by the Scientific and Technological Research Council of Turkey, 2219 International Postdoctoral Research Fellowship Program. Dr. O'Donovan is supported by MRC programme grant (G08005009) and an MRC Centre grant (MR/L010305/1). Dr. Rutten was funded by a VIDI award number 91718336 from the Netherlands Scientific Organisation. Drs Guloksuz and van Os are supported by the Ophelia research project, ZonMw grant number: 636340001. Dr. Arango was supported by the Spanish Ministry of Science and Innovation; Instituto de Salud Carlos III (SAM16-PE07CP1, PI16/02012, PI19/024); CIBERSAM; Madrid Regional Government (B2017/BMD-3740 AGES-CM-2); Fundación Familia Alonso and Fundación Alicia Koplowitz.

Ethical standards

The projects were approved by the Medical Ethics Committees of all participating sites and conducted in accordance with the Declaration of Helsinki. All respondents provided written informed consent and, in the case of minors, such consent was also obtained from parents or legal guardian.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request under the condition of the approval of the EUGEI and GROUP steering committees.

Declaration of Competing Interest

Celso Arango has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. Michael O'Donovan is supported by a collaborative research grant from Takeda Pharmaceuticals. Maria Paz Garcia-Portilla has been a consultant to and/or has received honoraria/grants from Angelini, Alianza Otsuka-Lundbeck, Instituto de Salud Carlos III, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, and SAGE Therapeutics.

Acknowledgements

The authors are grateful to the patients and their families for participating in the project. They also thank all research personnel involved in the GROUP project, in particular J. van Baaren, E. Veermans, G. Driessen, T. Driesen, E. van't Hag and J. de Nijs. All the DNA samples from Turkey were provided by the Ankara University Brain Research Center Biobank, that was supported by Ankara University Scientific Research Projects Coordination Unit (project no. 10A6055003, 2010).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2021.110440.

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