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The interaction between early life complications and a polygenic risk score for schizophrenia is associated with brain activity during emotion processing in healthy participants

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Abstract

Background. Previous evidence suggests that early life complications (ELCs) interact with polygenic risk for schizophrenia (SCZ) in increasing risk for the disease. However, no studies have investigated this interaction on neurobiological phenotypes. Among those, anomalous emotion-related brain activity has been reported in SCZ, even if evidence of its link with SCZ-related genetic risk is not solid. Indeed, it is possible this relationship is influenced by non-genetic risk factors. Thus, this study investigated the interaction between SCZ-related polygenic risk and ELCs on emotion-related brain activity.

Methods. 169 healthy participants (HP) in a discovery and 113 HP in a replication sample underwent functional magnetic resonance imaging (fMRI) during emotion processing, were categorized for history of ELCs and genome-wide genotyped. Polygenic risk scores (PRSs) were computed using SCZ-associated variants considering the most recent genome-wide association study. Furthermore, 75 patients with SCZ also underwent fMRI during emotion processing to verify consistency of their brain activity patterns with those associated with risk factors for SCZ in HP.

Results. Results in the discovery and replication samples indicated no effect of PRSs, but an interaction between PRS and ELCs in left ventrolateral prefrontal cortex (VLPFC), where the greater the activity, the greater PRS only in presence of ELCs. Moreover, SCZ had greater VLPFC response than HP.

Conclusions. These results suggest that emotion-related VLPFC response lies in the path from genetic and non-genetic risk factors to the clinical presentation of SCZ, and may implicate an updated concept of intermediate phenotype considering early non-genetic factors of risk for SCZ.

Introduction

Schizophrenia (SCZ) is a brain disorder associated with an high heritability reaching up to 80% (Owen, Sawa, & Mortensen, 2016; Sullivan, 2005) and complex genetic architecture. In particular, the largest genome-wide association study (GWAS) to date has tackled the genetic complexity of this disorder, identifying 287 independent genetic loci associated with its diagnosis (Trubetskoy et al., 2022). A commonly used strategy to shape a profile of such a complex genetic risk is the computation of a SCZ-related polygenic risk score (PRS) (Consortium, 2014; Purcell et al., 2009; Trubetskoy et al., 2022; Wray, Goddard, & Visscher, 2007), which sums the weighted effect size of GWAS-significant alleles on diagnosis and indexes the cumulative polygenic risk for SCZ for each individual. This method has often been used to investigate PRS association with disease-related phenotypes at biological and clinical levels (Cosgrove et al., 2017; Fusar-Poli et al., 2022; Lancaster et al., 2016; Walton et al., 2014).

Other evidence suggests that non-genetic factors such as complications during pregnancy, labor, delivery, and neonatal periods, also referred to as early life complications (ELCs) (Ursini et al., 2018) increase the risk for SCZ. (Cannon, Jones, & Murray, 2002; McNeil, Cantor-Graae, & Sjöström, 1994). More importantly, a recent report has indicated that exposure to ELCs increases the liability for SCZ explained by cumulative genetic risk for the disease, as indexed by PRS (Ursini et al., 2018). More recently, another study using a different method to evaluate ELCs failed to demonstrate their statistically significant interaction with PRS (Vassos et al., 2022).

An important topic in this field is the investigation of the relationship between risk factors of SCZ and biological phenotypes of relevance for the disorder. In this regard, previous literature has highlighted the concept of 'intermediate phenotypes', which are quantitative correlates of the illness linked with its genetic risk (Bertolino & Blasi, 2009), expressed in healthy relatives and individuals at clinical and genetic risk, and thus etiologically independent from state-related variables including pharmacological treatment, symptoms, and chronicity. Indeed, the relationship between putative intermediate phenotypes and genetic risk for SCZ should be best provided in healthy subjects to prevent the effects of confounding factors related to the state of the disease that might affect the biology of the brain, as done previously (Chen et al., 2018; Dimitriadis et al., 2021; Koch, Nyberg, Lundquist, & Kauppi, 2022; Miller et al., 2018).

Crucial phenotypes of SCZ are those related to anomalies in emotion processing (Kohler & Martin, 2006). This domain is modulated by genetic variation (Drabant et al., 2006; Hariri et al., 2005, 2002; Lo Bianco et al., 2013; Smolka et al., 2005) possibly relevant to SCZ (Shifman et al., 2004; Williams, Owen, & O'Donovan, 2007) and includes both simple and complex subprocesses, by which emotions are perceived, recognized, as well as regulated and managed (Green et al., 2008). Several functional imaging studies have convergently indicated in SCZ abnormal activation of different brain regions during emotion processing, including the ventrolateral prefrontal cortex (VLPFC), as well as the dorsolateral prefrontal cortex, the amygdala and the hippocampus (Dyck, Loughead, Gur, Schneider, & Mathiak, 2014; Dzafic, Burianová, Periyasamy, & Mowry, 2018; Etkin, Büchel, & Gross, 2015; Frank et al., 2014; Mier et al., 2014; Spilka & Goghari, 2017). However, the directionality of such abnormalities is not always consistent in the literature. In fact, either hyper-(Dyck et al., 2014; Dzafic et al., 2018; Taylor, Liberzon, Decker, & Koeppe, 2002) or hypo-activation (Anticevic et al., 2012; Paradiso et al., 2003; Spilka & Goghari, 2017; Taylor et al., 2012) of the emotion-related brain network have been reported, which may partly rely on differences in task and study design, as well as on state-related characteristics of patients. Furthermore, it is unclear if abnormal brain processing of emotions in SCZ is linked with genetic risk for the disorder and may be considered an intermediate phenotype for the disease. For example, results in at-risk individuals are not consistent and indicate either lack of anomalies (Martin et al., 2020; Rasetti et al., 2009; van Donkersgoed, Wunderink, Nieboer, Aleman, & Pijnenborg, 2015) or abnormal activity in brain regions included in the emotion-related brain network (Park et al., 2016; van Buuren, Vink, Rapcencu, & Kahn, 2011; Wang et al., 2018; Wolf et al., 2015). Furthermore, findings from a recent meta-analysis indicate a lack of differential brain response between at-risk individuals and healthy participants (HP) (Fiorito et al., 2022). Accordingly, results on the association between brain emotion processing and polygenic risk for SCZ are sparse. To our knowledge, such a link has been reported in only one study using a limited sample size, in which a positive correlation of prefrontal, amygdala and insula activity with a SCZ PRS was found during anger perception, which shifted to a negative correlation during perception of happiness (Dzafic et al., 2018). On the other hand, another study using a larger sample size did not find any correlation between PRS for this disorder and brain processing of emotional stimuli, which was instead associated with a single nucleotide polymorphism (SNP) (Erk et al., 2017). Taken together, all these findings suggest that it is doubtful that brain activity during emotion processing falls within the standard definition of intermediate phenotype for SCZ because of the lack of solid evidence on its association with at-risk conditions and disease-related genetics. On the other hand, another interpretation may be based on the hypothesis that phenotypes crucially linked with SCZ are expressed in presence of the interaction between genetic and non-genetic factors of risk (Ursini et al., 2018). As a consequence, with the currently available resolution and statistical power, it is also possible that these phenotypes are not detectable in individuals at genetic risk when they are not exposed to such non-genetic factors.

The aim of the present study was to investigate the interaction between ELCs and polygenic risk factors for SCZ on physiological brain response during emotion processing. With this aim, we investigated in a discovery analysis whether a PRS, based on genetic risk variants derived from the largest SCZ GWAS to date (Trubetskoy et al., 2022), interacts with ELCs in modulating brain response in HP during tasks eliciting either emotional perceptual processing (implicit processing) or explicit emotional evaluation (explicit processing) (Blasi et al., 2009a; Blasi et al., 2009b; Quarto et al., 2018). To strengthen the findings obtained in the discovery sample, we then performed two further parallel investigations: first, we used an independent sample of HP to replicate the results found in the discovery sample. Second, we performed a further analysis to verify whether the pattern of brain response found in the discovery and replication analyses in HP was coherent with those associated with the effect of the diagnosis of SCZ.

Materials and methods

Participants

Discovery sample of HP

One hundred sixty-nine HP (Table 1) were included in the discovery sample. All participants were white Caucasians from the region of Puglia, Italy (see online Supplementary material).

All HP were genotyped for variations associated with SCZ (Trubetskoy et al., 2022) and the McNeil–Sjöström scale (McNeil et al., 1994) was used to assess the presence of serious ELCs, as described in previous work (Ursini et al., 2018). Furthermore, they underwent fMRI scanning during a task eliciting emotion processing (Blasi et al., 2009a; Quarto et al., 2016; Taurisano et al., 2013).

Replication sample of HP

113 HP (76 with ELCs) (Table 1) were used as a replication sample in this study (see online Supplementary material). Genotyping and assessment of the presence of serious ELCs were performed as for the discovery sample. All these individuals performed a

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Table 1. Demographics and clinical variables of the samples of the study

				HP-discovery sample vs SCZ	
	HP-discovery sample ($n = 169$)	HP-replication sample ($n = 113$)	SCZ ($n = 75$)	$\chi 2$	*P*
Age, years (mean ± SD)	26.8 ± 6.9	28.6 ± 8.5	32.1 ± 8.2		<0.001
Gender, n					
Male	85	48	52	7.64	0.006
Female	84	65	23		
SES	38.5 ± 16.05	nd	28.5 ± 14.3		<0.001
Premobid IQ	115.12 ± 3.5	107.9 ± 9.9	107.10 ± 7.5		<0.001
Olanzapine equivalents			17.3 ± 6.8		
PANSS total score			85 ± 21.7		

HP, healthy participants; SCZ patients with schizophrenia; SES, socioeconomic status; premorbid IQ premorbid intelligence quotient; PANSS, Positive and Negative Syndrome Scale.

task eliciting emotion processing during fMRI (Hariri, Bookheimer, & Mazziotta, 2000).

Sample of SCZ

Seventy-five white Caucasian Apulian SCZ (Table 1), as diagnosed with the SCID, were used to investigate the effect of diagnosis on brain activity during emotion processing (see online Supplementary material). They also underwent fMRI scanning during the same emotion task used for the discovery sample (Blasi et al., 2009a; Quarto et al., 2016; Taurisano et al., 2013).

All participants provided written informed consent to the study fully explained the procedure of them. The study was approved by the Italian local Institutional Review Board, as well as by the Institutional Review Board of the Intramural Program of the National Institute of Mental Health.

Computation of PRS

After genotyping (see online Supplementary material), PRS for each HP of the discovery and replication samples was calculated using the sum of an individual's statistically independent risk alleles, weighted by their effect size (odds ratio) derived from the Psychiatric Genomics Consortium Wave 3 (PGC3) SCZ GWAS (Trubetskoy et al., 2022). To prevent any bias related to sex in the PRS calculation, only autosomal SNPs were included in the analysis, according to the standard procedure for PRS calculation (Consortium, 2014; Purcell et al., 2009; Trubetskoy et al., 2022). We performed a linkage disequilibrium (LD) clumping of the SNPs, according to parameters used by PGC (Consortium, 2014; Trubetskoy et al., 2022), defining LD-independent SNPs as those with low LD ($r2 < 0.1$) within a 500 kb window. A PRS (PRS_GWA) was computed as done previously (Pergola et al., 2019) using genome-wide significant ($p < 5e\text{-}08$) SNPs, according to PGC3 (Trubetskoy et al., 2022), present in our dataset ($n = 207$). A further score was calculated in the discovery sample, using genetic variants whose statistics for the association with diagnosis of SCZ was at $p < 0.05$ (PRS_05,), in order to include in such PRS genetic variants that are likely not key for the pathophysiology of this brain disorder.

Since the discovery dataset was included in the PGC3 study, we used the leave-site-out summary statistics for this sample. All PRSs were adjusted for genotyping batch and for the first 10 genomic principal components to account for population stratification within the sample (Consortium, 2014; Trubetskoy et al., 2022). Marginalized PRSs were transformed in units of standard deviations from the mean.

Assessment of ELCs: the McNeil- Sjöström scale

ELCs (Ursini et al., 2018) were evaluated in both discovery and replication samples using a well-standardized and validated questionnaire (Nicodemus et al., 2008), based on all the items scored with the McNeil–Sjöström scale for obstetric complications (McNeil et al., 1994), administered to the mothers of HP. ELCs are classified according to time of onset and severity. With regard to the latter, a severity level between 1 and 6 was assigned to each ELCs, based on the degree of inferred potential harm to the offspring's central nervous system (Ursini et al., 2018). ELCs with severity level ⩾4 are considered potentially harmful or relevant factors for fetal stress (Ursini et al., 2018). Using a previously published method (Ursini et al., 2018), we defined a positive history for serious ELCs based on the presence of at least one serious ELC (severity level ⩾4). On this basis, 111 out of 169 HP had a positive history of serious ELCs in discovery sample while in the replication sample those with a positive history of serious ELCs were 76 out of 113 (see online Supplementary table 1 for the description of available information on ELCs).

The frequency of ELCs in both samples is likely higher compared with the general population, as reported in previous work (Ursini et al., 2018). This is likely related to the fact that we included in our samples only participants with certain information about the presence or absence of ELCs, since – when using a questionnaire with many items – it is often more challenging to exclude at least one serious ELCs than confirm its presence (for example, if a mother was not able to clarify whether her newborn was just 'pale' or 'anoxic', we had to exclude the subject from the sample if there are no other indicators of ELCs, while we were able to include him/her in the sample when other clear ELCs, like preeclampsia, IUGR, etc. are reported).

fMRI experimental paradigm and data acquisition for the discovery and SCZ samples

The event-related fMRI paradigm (Blasi et al., 2009b; Quarto et al., 2016; Taurisano et al., 2013) consisted of two runs: each

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run presented angry, fearful, happy, and neutral facial expressions from a validated set of facial pictures (NimStim, http://www.macbrain.org/resources.htm) (Tottenham et al., 2009). During one run (emotional perceptual processing: implicit processing), participants identified the sex of each face. In the other run (explicit emotional evaluation: explicit processing), they had to decide whether they would like to 'approach' or 'avoid' the face (see online Supplementary materials).

Blood Oxygen Level Dependent (BOLD) fMRI was performed on a GE Signa 3 T scanner while participants performed the task (see online Supplementary material).

fMRI experimental paradigm and data acquisition for the replication analysis

The fMRI paradigm for the replication sample consisted in a face matching task, which has been used in several previous studies (Hariri et al., 2000, 2002, 2005). Participants are presented with blocks of trials that either ask them to decide which of two faces presented on the bottom of the screen match the face at the top of the screen, or which of two shapes presented at the bottom of the screen match the shape at the top of the screen. The faces have either an angry or fearful expression. A complete description of the task can be found in previous published papers (Hariri et al., 2000).

Also for the replication sample, BOLD fMRI was performed on a GE Signa 3 T scanner during task performance (see online Supplementary material).

Data analysis

Demographics and behavioral data

ANOVAs and $\chi 2$ were used to assess distribution of demographic variables between groups in the discovery, replication and SCZ samples. A repeated-measures ANCOVA, with ELCs and PRS as independent factors, and the two tasks as well as the four facial expressions as repeated-measures factors, was used to investigate the interaction between ELCs and PRS on reaction time data. Furthermore, a repeated-measures ANCOVA, with ELCs and PRS as independent factors, and the four facial expressions as repeated-measures factors, was performed to investigate the interaction between ELCs and PRS on the number of avoided faces. Age, sex, premorbid IQ, and SES were used as covariates of no interest.

fMRI data analysis

Discovery analysis

Analysis of the fMRI data was completed using Statistical Parametric Mapping 12 (SPM12, Wellcome Department of Cognitive Neurology, London, UK). After preprocessing of images (see online Supplementary material), in a first-level, single-subject analysis, linear contrasts were computed producing t statistical maps at each voxel for the four task conditions (corresponding to happy, angry, fearful, and neutral facial expressions of stimuli used in the event-related task) compared with the baseline condition (crosshair).

All individual contrast images were then entered in second-level random-effects analyses at the group level. First, a full factorial general linear model, covarying for age, sex, Premorbid IQ, and SES, was performed in HP to investigate the main effect of ELCs, of PRSs, their interaction, as well as their potential interactions with task and facial expressions. Such investigation was first performed using PRS_GWA, and then separately repeated with PRS_05.

All analyses were constrained by a mask obtained by combining group activation maps associated with the processing of each facial expression during each task and a gray matter mask implemented in the WFU PickAltas (http://fmri.wfubmc.edu/software/PickAtlas). The statistical threshold was set at $p < 0.05$ minimum cluster size (k) = 10, corrected for multiple comparisons using Threshold-Free Cluster Enhancement (TFCE-FWE<0.05) (Smith & Nichols, 2009). Then, percent signal change from the cluster associated with a PRS_GWA by ELCs interaction was extracted with MarsBar (https://www.nitrc.org/projects/marsbar/) and entered in Pearson's correlation tests, performed with IBM SPSS 25.0, to investigate its statistical relationship with PRS in individuals with and without severe ELCs separately.

Replication analysis

Also in the replication sample, analysis of the fMRI data was completed using SPM12. After preprocessing (see online Supplementary material), in the first-level analysis, matching vs resting were modeled using a box car convolved with the hemodynamic response function at each voxel. Head movement parameters obtained from the realignment procedure were included in the model as covariates, taking into account the effects of subject motion. A contrast map was generated for each individual using the beta value of face matching stimulus *v.* fixation cross-hair at each voxel.

Thus, we focused the group analysis on a region-of-interest (ROI) defined with MarsBar (https://www.nitrc.org/projects/marsbar/), using a sphere with a radius of 20 mm and centered on the activation peak of the cluster associated with a ELCs-PRS_GWA interaction in the discovery sample. In more detail, we extracted BOLD signal change from this ROI, which was used as a dependent variable, with ELCs (yes/no) and PRS as factors of interest and age, sex and premorbid IQ as covariates of no interest. Furthermore, Pearson's correlation test was used to investigate the relationship between BOLD signal change and PRS in individuals with and without severe ELCs separately.

Effect of diagnosis of schizophrenia

In a further analysis, HP of the discovery sample were compared with SCZ with ANCOVA to verify coherence of the brain imaging phenotype associated with the PRS_GWA by ELCs interaction in HP with those of full-blown disease. Again, we defined a 20 mm radius spherical ROI using MarsBaR, centered on the activation peak of the cluster associated with a ELCs-PRS_GWA interaction in the discovery sample. Given the aim of this analysis and the results of the ELCs-PRS_GWA interaction in HP, the interaction between diagnosis and task and/or emotion was not explored, even if these latter factors were inserted in the statistical design. Age, sex, premorbid IQ, and SES were also added as factors of no interest. Given that here the investigation was focused on the effect of diagnosis instead of the interaction between PRS and ELCs, a TFCE-FWE correction at $p < 0.05$ was used.

Results

Demographics and behavioral data

T-tests or χ^2 in the discovery and replication sample revealed homogeneous distribution of age, sex, premorbid IQ and SES between HP with and without an history of serious ELCs (all $p > 0.05$). There were no effects of PRSs, ELCs, of their interaction,

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as well as of their interaction with task and/or facial expression on reaction time (all $p > 0.05$). Furthermore, no significant main effects of PRSs, ELCs, of their interaction, as well as of their interaction with facial expressions were found on the number of avoided faces (all $p > 0.05$). With regard to the analysis in the SCZ sample, age, sex, premorbid IQ and SES were significantly different between HP and SCZ (all $p < 0.001$).

Imaging data

Discovery analysis

A general linear model performed in HP did not reveal significant main effects of PRS_GWA or ELCs on brain activity. Instead, their interaction was significant in Left VLPFC (x, y, z: −52, 16, 16; k: 24; Z: 3.89) (BA44) (Fig. 1) (see also online Supplementary Figure 1 for whole brain results). No further interactions with tasks or/and facial expression were found. Post-hoc investigation on signal change extracted from the significant VLPFC cluster indicated a positive correlation between PRS_GWA and VLPFC activity in participants with a history of serious ELCs (r = 0.269; $p = 0.008$), while the correlation was negative in participants without history of ELCs (r = −0. 433; $p < 0.001$). Further separate ANCOVA using PRS_05 did not indicate significant PRS by ELCs interaction on brain activity during emotion processing.

Replication analysis

ANCOVA on signal change, extracted from the ROI centered on the peak of activity of the cluster associated with a ELCs-PRS_GWA interaction in the discovery analysis, revealed an interaction between PRS_GWA and ELCs also in replication sample (F = 7.42; $p = 0.008$). Moreover, Pearsons' test indicated a positive correlation between PRS_GWA and VLPFC activity in participants with a history of serious ELCs ($r = 0.277$; $p = 0.018$), while such a relationship was not significant in participants without a history of ELCs ($r = -0.198$; $p = 0.258$) (Fig. 2) (see also online Supplementary Table 2 for whole brain results in this sample).

Effect of diagnosis of schizophrenia

There was an effect of diagnosis on the ROI centered on the activation peak of the cluster associated with a ELCs-PRS_GWA interaction ($P_{TFCE-FWE}$:0.016, x,y,z: −59, 8, 1) (BA 44) (Fig. 3a), with greater activity in SCZ than HP (Fig. 3b and online Supplementary figure 2).

Discussion

The results of this study suggest that genetic and non-genetic factors interacting on diagnosis of SCZ (Ursini et al., 2018) have also a combined effect on physiological brain response during emotion processing. Paramount in this context is VLPFC activity, which was associated in HP with the interaction between polygenic risk for SCZ and ELCs in two independent samples. Furthermore, VLPFC response during emotion processing was also anomalous in SCZ. Taken together, these results suggest a brain phenotype on the biological pathway connecting genetic and non-genetic risk with the clinical presentation of this brain disorder.

We found that the association between left VLPFC response during emotion processing and PRS is modulated in HP by ELCs in the discovery analysis. This interaction was present when investigating PRS_GWA, but not when looking at PRS_05. Importantly, we replicated such an interaction in an independent American sample of HP. PRS_GWA is a genetic score computed using genome-wide significant SCZ-associated alleles (Trubetskoy et al., 2022), which raises the possibility that only cumulative effect of SNPs linked the most with pathophysiological mechanisms of the disorder are relevant in modulating brain activity during emotion processing in interaction with ELCs, while adding more 'genetic noise' to the genetic features most associated with SCZ implicates a loss of such an association. This is consistent with previous findings indicating that only the PRS computed with the variants with the most significant association with SCZ interacts with ELCs in affecting SCZ case–control status (Ursini et al., 2018) and early neurodevelopmental outcomes (Ursini et al., 2021).

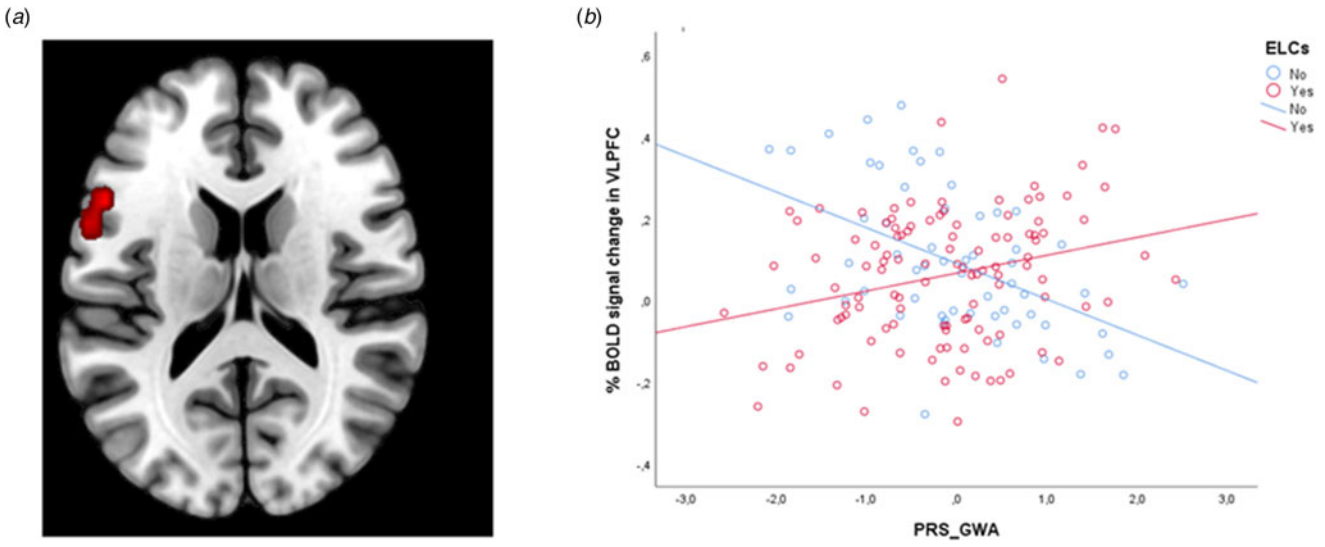

Figure 1. Discovery sample: (A) Axial section of the brain showing the cluster in VLPFC where an interaction between PRS_GWA and ELCs was present; (B) scatterplot of % signal change extracted from the cluster represented in A. as a function of PRS_GWA and ELCs. See results for statistics. PRS_GWA: polygenic risk score genome-wide associated with diagnosis of schizophrenia.

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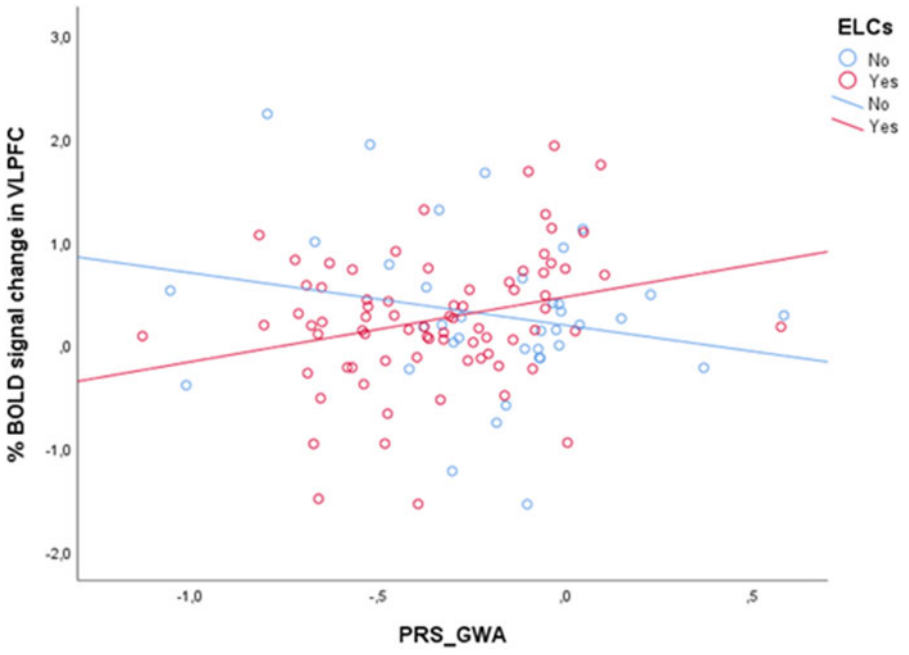

Figure 2. Replication sample: scatterplot of % signal change extracted from the 20 mm ROI centered on the peak voxel associated with a PRS_GWA by ELCs interaction in the discovery analysis. See results for statistics. PRS_GWA: polygenic risk score genome-wide associated with diagnosis of schizophrenia

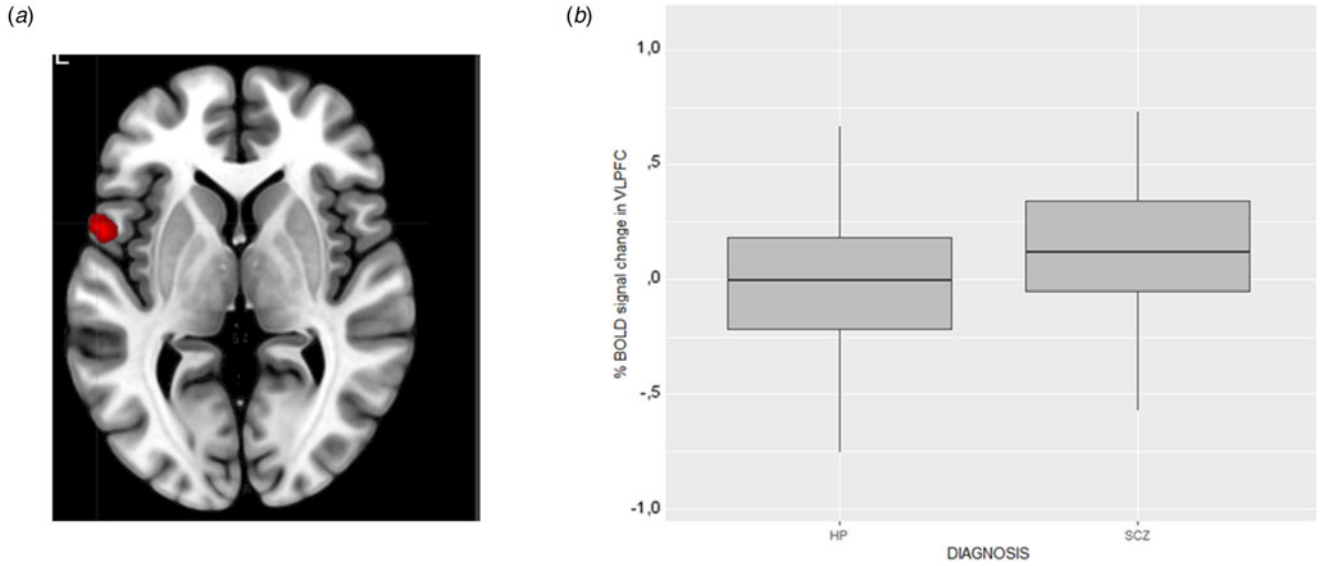

Figure 3. (A) Axial section of the brain showing the cluster in left VIPFC associated with a main effect of diagnosis during emotion processing; (B) Mean BOLD signal change in SCZ and HP extracted from this cluster shown in A. See results for statistics. PRS_GWA: polygenic risk score genome-wide associated with diagnosis of schizophrenia. HP: healthy participants; SCZ: patients with schizophrenia

Further analysis of left VLPFC BOLD response indicated that, in the discovery and replication samples, it was positively correlated with PRS_GWA in presence of ELCs, which suggests that VLPFC activity increases with the increase of cumulative genetic risk for SCZ, but only in the context of perinatal, non-genetic risk factors for the disease (Ursini et al., 2021). On the other hand, we found in the discovery sample that the correlation between VLPFC response and PRS_GWA was negative in absence of ELCs. Differential relationships between PRS and brain activity in presence and absence of ELCs may be interpreted in the context of the differential susceptibility framework, (Belsky, 2007; Belsky & Pluess, 2009), which is closely related to the concept of biological sensitivity to context (Ellis, Essex, & Boyce, 2005). According to this framework, individual attributes (such as genetic features associated with brain disorders) implicate disadvantageous outcomes in high-stress environments (e.g. ELC), while they are associated with even advantageous outcomes in favorable environmental conditions (Belsky, 2007; Belsky & Pluess, 2009). However, the negative correlation between left VLPFC activity and PRS_GWA in absence of ELCs was not statistically significant in the replication analysis, suggesting that further investigation is needed to confirm this relationship.

VLPFC is part of the emotion brain network (Etkin et al., 2015; Phillips, Drevets, Rauch, & Lane, 2003) and previous literature posits that it plays a role in attributing emotional significance to environmental stimuli and in affective state production

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(Phillips et al., 2003). Indeed, abnormal activity in this brain region has been found in patients with SCZ in terms of either hyper- (Dyck et al., 2014) or hypo-activity (van der Meer et al., 2014). Interestingly, BA 44 has also been specifically associated with severe ELCs in patients with SCZ, with bipolar disorder and in HP (Wortinger et al., 2022).Thus, our findings in HP suggest that the interaction between genetic and non-genetic risk factors for SCZ modulates activity in a brain region involved in basic processing of emotions and abnormally activated in patients with this brain disorder. To our knowledge, there are no studies to date investigating the interaction between SCZ-related polygenic risk and non-genetic factors of liability on neurobiological phenotypes relevant to this brain disease. On the other hand, results on the association between polygenic risk for SCZ and brain activity during emotion processing are sparse (Dzafic et al., 2018; Erk et al., 2017). In particular, only one study using a limited sample size of healthy individuals reported emotion-specific correlation between a PRS for SCZ and brain activity (Dzafic et al., 2018). Indeed, another study using a large sample of individuals did not find an association between emotion processing-related brain response and cumulative genetic risk for the illness (Erk et al., 2017). Results from a recent meta-analysis (Fiorito et al., 2022) appear to be consistent with the findings of this latter report. More to the detail, this study did not find any whole-brain difference in activity during emotion processing between HP and individuals at-risk for psychosis considering seventeen previous reports (Fiorito et al., 2022). Thus, most of the previous literature on this topic is in line with our findings indicating a lack of association between polygenic risk for SCZ and emotion-related brain activity. However, our results also indicate that this association can be detected when non-genetic factors of liability for this brain disorder are taken into account. This finding may be interpreted in the context of the concept of incomplete penetrance (Gottesman & Shields, 1967). According to this explanatory framework, individuals with a genetic environment of risk may or may not express a related phenotype, which may be instead elicited when other factors of risk are present. Thus, it is possible that ELCs increase penetrance of polygenic risk on brain correlates associated with emotion processing in SCZ. Indeed, this aspect may implicate an updated concept of intermediate phenotype, which should also consider the interaction between genetic and non-genetic factors to discover crucial biological correlates of the disorder.

The comparison that we performed between HP and SCZ is consistent with, and adds further evidence to, the relevance of the PRS-ELCs interaction that we found in HP for full-blown SCZ. Indeed, it is well established that brain activity during emotion processing is anomalous in this brain disorder (Kohler & Martin, 2006). However, inconsistent directionality of the findings has been reported across studies, showing either hyper- or hypo-activation in SCZ compared with HP, which may be explained by different factors including task and patient characteristics. Here, we found that activity in left VLPFC is greater in SCZ than HP, which appears to be consistent with our finding that the interaction between genetic and non-genetic risk factors for SCZ tends to increase response in this brain region in HP. Taken together, these results suggest that VLPFC response during emotion processing is crucial for pathophysiological aspects of SCZ and linked with risk factors for the disorder. Furthermore, they are also consistent with the neurodevelopmental hypothesis of SCZ (Weinberger, 1987), which posits that adverse events occurring during early life may lead to dysfunction of specific neural networks that would account for SCZ-related phenotypes in later life. This hypothesis calls for further studies aimed to elucidate the biological mechanisms underlying such interaction, which may include epigenetic signals as those related to methylation of DNA (Jaffe et al., 2016) and transcriptomic changes in placenta (Ursini et al., 2023)

Some limitations should be considered in this study. First, we did not investigate the interaction between PRS and ELCs in SCZ. However, our choice was to investigate this interaction in HP to avoid state-related confounding effects, including psychopharmacological treatment, symptoms, and chronicity. A second limitation is that the frequency of ELCs in our sample is likely higher compared with those in the general population. This may be related to the fact that the inclusion of only participants with certain information about the presence or absence of ELCs may result in a sample with a higher frequency of ELCs compared with the general population, since it is often more challenging to exclude at least one serious ELC than confirm its presence, particularly when using maternal interviews. Indeed, because the objective of our study is to test a gene-environment interaction, we have decided to include in our sample only participants with certain information about the presence or absence of ELCs. Another limitation is that ELCs have been assessed using maternal interviews rather than medical records, which implicates a lack of detailed information about all the ELCs occurring in each individual. This aspect makes it not possible to disentangle the role of a specific ELC in the interaction with PRS, as well as to precisely weight the different level of ELCs exposure of each individual. However, consistent literature indicates that ELCs usually do not occur in isolation (Davies, Bell, & Bhattacharya, 2016; Feghali, Caritis, Catov, & Scifres, 2016; Murata et al., 2022; Rasmussen, Ebbing, & Irgens, 2017; Yang & Wu, 2022). Thus, it is possible that the pooled effect of different complications acting during the peri-natal period is crucial to increase risk for pathophysiological mechanisms relevant to SCZ in interaction with the cumulative effect of genetic features linked with this brain disorder.

In conclusion, our results suggest that ELCs converge with genomic risk factors in affecting anomalies of emotional processing relevant to SCZ. In this sense, further studies should consider the interaction between genetic and non-genetic factors to identify intermediate phenotypes of SCZ, which are key to add new knowledge on pathophysiological mechanisms for this brain disorder.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0033291724000011.

Authors' contributions. GB conceived and designed the study paradigm. LAA, TQ, and LF collected the fMRI data. GU collected the genetic and ELCs data. GU, QC, and DRW collected, analyzed and provide fMRI and genetic data of the replication sample. RM and ST contributed to genotypization procedures. FM and ED contributed to the enrollment. VDT, LF, RP, TQ, and GP analyzed the fMRI data. LS and GCK analyzed the genetic data. RP provided contributions to the statistical analysis. VDT drafted the initial manuscript, and GB provided critical revisions. AR, GP, and AB revised the article. All of the authors discussed the results, commented, and approved the final manuscript for submission.

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