**Supplementary Methods**

**Participants**

***Discovery sample***

The Structured Clinical Interview (SCID) based on the Diagnostic and Statistical Manual of Mental Disorders-IV (APA, 2000) was used to exclude any psychiatric disorder. Exclusion criteria were the presence of any significant neurological or medical condition revealed by clinical and magnetic resonance imaging evaluation, history of head trauma with loss of consciousness, and pharmacological treatment or drug abuse in the past year. All participants underwent the Hollingshead scale (Hollingshead, 1975) for the evaluation of socio-economic status (SES) and the Italian version of the Wide Reading Achievement Test (Wilkinson *et al.*, 2006) (WRAT) to assess premorbid IQ.

*Replication sample*

All participants were white Caucasians and were enrolled in the Clinical Brain Disorders Branch Sibling Study of schizophrenia at the National Institute of Mental Health, Bethesda, MD, USA. All participants were assessed with the Structured Clinical Interview for DSM-IV (APA, 2000) to exclude any psychiatric disorder. Exclusion criteria were the same as those used for the discovery sample. Furthermore, the Hollingshead scale and the WRAT were also administered to this sample.

*Sample of SCZ*

Exclusion criteria were the same as those used for **HP.** The Hollingshead scale and WRAT were also administered to this group of individuals.

*Genotyping*

**HP** underwent venipuncture for subsequent DNA extraction from peripheral blood mononuclear cells. Approximately 200 ng of DNA were used for genotyping. To genotype our sample, we used Illumina HumanHap550K/610-Quad Bead Chips (San Diego, California). Briefly, each sample was whole-genome amplified, fragmented, precipitated, and resuspended in appropriate concentrations of hybridization buffer. Denatured samples were hybridized on prepared Illumina Human550K/610-Quad Bead Chips. After hybridization, the Bead Chip oligonucleotides were extended by a single labeled base, which was detected by fluorescence imaging with an Illumina Bead Array Reader. Normalized bead intensity data obtained for each sample were loaded into the Illumina Genome Studio (Illumina, v.2010.1) with cluster position files provided by Illumina, and fluorescence intensities were converted into SNP genotypes.

*fMRI experimental paradigm and data acquisition for the* ***discovery sample and patients with schizophrenia***

The event-related fMRI paradigm (Blasi *et al.*, 2009b, Quarto *et al.*, 2016, Taurisano *et al.*, 2013) consisted of two runs: each 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). The order of stimuli was randomly distributed. However, the same stimuli were presented in both runs in the same order. During one run (emotional perceptual processing: implicit processing), **participants** identified the gender 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. From stimulus appearance, 2 s were allowed for behavioral responses. The presentation of the two runs was counterbalanced across **participants**. Each stimulus was presented for 500 ms, with the interstimulus interval randomly jittered between 2 and 7 s. The total number of stimuli was 144: 30 angry, 39 fearful, 37 happy, and 38 neutral faces. The duration of each run was 6 min 8 s. A fixation crosshair was presented during the interstimulus interval.

Blood Oxygen Level Dependent (BOLD) fMRI was performed on a GE Signa 3T scanner (repetition time, 2000 ms; echo time, 28 ms; 26 interleaved axial slices; thickness, 4 mm; gap, 1 mm; voxel size, 3.75 × 3.75 × 5; flip angle, 90°; field of view, 24 cm; matrix, 64 × 64) while participants performed the task. The first four scans were discarded to allow for signal saturation. Stimuli were presented via a back-projection system and responses were recorded through a fiber optic response box which allowed measurement of behavioral data.

*fMRI experimental paradigm and data acquisition for the replication sample*

Each subject underwent BOLD fMRI on a GE Signa 3-T scanner using gradient echo BOLD-EPI pulse sequence (TR/TE = 2000/28 millisecond, flip angle = 900, field of view = 24 cm, 64 x 64 matrix). One hundred forty-four whole brain images comprising 24 (4 mm thick, 1 mm gap) axial slices covering the entire cerebrum and most of the cerebellum were acquired for each subject while they performed the Face Matching task.

*Preprocessing of fMRI data for the discovery sample and SCZ*

Images for each subject were realigned to the first volume in the time series and movement parameters were extracted. Subjects with excessive head motion (>2 mm of translation, >1.5° rotation) were excluded if just one volume in the fMRI time series exceeded the movement threshold. On this basis, we excluded 11 healthy HS and 8 SCZ, who were not included in Table 1. Images were slice timing corrected, re-sampled to a 3.75 mm isotropic voxel size, spatially normalized into standard stereotactic space (Montreal Institute on Neurology, MNI, template), and smoothed using an 8 mm full-width half-maximum isotropic Gaussian kernel. fMRI responses were modeled using a canonical hemodynamic response function and temporally filtered using a high-pass filter of 128 Hz to minimize scanner drift. Six subject-specific movement parameters, obtained from the realignment procedure, were included in the general linear model (GLM) as covariates, taking into account the effect of subject motion

*Preprocessing of fMRI data for the replication sample*

The images were pre-processed in SPM12 (http://www.fil.ion.ucl.ac.uk/spm ) using standard procedures. Briefly, images were realigned to the first image of the scan run using INRIalign, spatially normalized to a 3 × 3 × 3 mm3 voxel size into a standard stereotactic space (MNI template) using affine and nonlinear transformation and smoothed using an 8-mm full width half maximum isotropic three-dimensional Gaussian kernel. Data sets were individually examined to ensure head motion was less than 2 mm translation and less than 1.5° rotation.

All fMRI data were individually examined and carefully screened for data quality using a variety of procedures including visual inspection for image artifacts, estimating indices for ghosting artifacts, signal-to-noise ratio across the time series, and head motion (data from participants with head motion greater than 2 mm translation and/or head rotation greater than 1.5° were excluded).

**Supplementary Tables**

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Discovery Sample** | **Replication Sample** |
| **Event scored ad ELC** | **McNeil-S. scale level** | *%* | *%* |
| Substance use (alcohol, drug) | 4,5,6 | 3 |  |
| Smoking | 4, 5 |  | 15.8 |
| Prescription drugs, treatments (including radiation) during pregnancy | 4,5 | 6 |  |
| Severe illness during pregnancy |  | 7.9 | 2.6 |
| RH immunization | 5 | 4 | 1.3 |
| Bleeding, hemorrhage during pregnancy | 4,5 | 6 | 13.2 |
| Threatened abortion | 4,5 | 6 |  |
| Preeclampsia, eclampsia | 4,5,6 | 1.5 | 3.9 |
| Amniotic fluid infection | 5 | 1.5 |  |
| Premature rupture of fetal membrane not followed by delivery | 5 |  | 2.6 |
| Abnormal presentation at delivery | 4,5 | 6 | 7.9 |
| Cesaerean section | 4,5 | 27.6 | 23.7 |
| Forceps | 4,5,6 |  | 17.1 |
| Umbilical cord complications and other delivery problems | 4,5 | 6 | 3.9 |
| Maternal anesthesia | 4,5 |  | 17.1 |
| Precipitous labor | 4,5 | 16.9 | 22.4 |
| Prolonged labor | 4 | 6 | 14.5 |
| Second twin or triplet birth | 4 | 16.9 |  |
| Pre-term, underweight, SGA | 4,5,6 | 27.6 | 18.4 |
| Post-term, postmature | 4 | 3 |  |
| Neonatal severe distress | 4,5,6 |  | 10.5 |
| Placed intensive care | 4 | 7.9 | 1.3 |
| Hyperbilirubinemia | 4,5 |  | 5.3 |
| Newborn anomalies | 4 |  | 2.6 |
| Toxoplasmosis | 4 | 3 |  |
| Pre-labor Rupture of the Membranes>24h before delivery | 4 | 4 |  |

Supplementary table 1: Grouped ELCs in the discovery, confirmatory, and replication sample. Reported is the percentage of individuals with grouped ELCs detected in each dataset. For each ELC, we report the McNeil-Sjöström scale severity levels assigned to that ELC. Only severe ELCs, potentially harmful for fetal brain, are reported (McNeil-Sjöström scale severity level 4, 5, or 6). More than one ELCs may have occurred in each individual. A detailed obstetrical history was not available for all the individuals; however, the discovery and replication samples only include individuals for whom it was possible to establish the presence of at least one severe ELC or the absence of any severe ELC.

|  |  |  |  |
| --- | --- | --- | --- |
| MNI coordinates | BA | K | Z |
| 21 –73 -5 | 18, 19, 17 | 114 | 3.62 |
| 6 23 64 | 6 | 77 | 3.40 |
| -33 8 -17 | 13, 38 | 187 | 3.38 |
| -3 47 34 | 8,9 | 128 | 3.07 |
| -36 14 34 | 8 | 59 | 2.67 |
| -45 26 -14 | 44,45,47 | 52 | 2.57 |

Supplementary table 2: Statistics showing the interaction between PRS\_GWA and ELCs in the replication sample at p<0.05, uncorrected.

**Supplementary Figures**

**Immagine che contiene testo, schermata

Descrizione generata automaticamente**

Supplementary figure 1. Brain map showing the interaction between PRS\_GWA and ELCs at p<0.001, uncorrected in the discovery sample. At this statistical threshold, there was an interaction between PRS\_GWA and ELCs in left Cerebellum (-40, - 56, - 25) and left inferior occipital gyrus (-37, -90, 1) The VLPFC cluster reported in the manuscript was the only one surviving to TFCE correction.

**Immagine che contiene schizzo, testo, diagramma, disegno

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Supplementary figure 2 Scatterplot showing mean signal changes in SCZ and HP extracted from the VLPFC cluster associated with a Main effect of Diagnosis.