**Supplemental Material**

***Genotyping***

Blood was collected for genotyping and Genome-wide SNP data was available for all 79 participants. Blood samples were collected using standard operating procedures and stored using a laboratory information management system at the Wellcome Trust Clinical Research Facility Genetics Core, Edinburgh (www.wtcrf.ed.ac.uk). DNA samples were genotyped by the WT-CRF using Illumina HumanOmniExpressExome-8 v1.0 DNA Analysis BeadChip and Infinium chemistry. Genotypes were processed using GenomeStudio Analysis Software v2011.1 (Gunderson, 2009).

***Gyrification Indices – Schaer’s Method***

Schaer’s 3-D method (Schaer *et al.* 2008) has been employed to study gyrification across various conditions such as first episode psychosis (Janssen *et al.* 2009), depression (Zhang *et al.* 2009), learning disabilities (Zhang *et al.* 2010) and 22q11 deletion syndrome (Schaer *et al.* 2009). With the gray–white interface constructed via surface registration and cortical inflation from the Freesurfer workflow, a pial surface is first obtained by constructing a set of lines perpendicular to the gray–white interface. A morphological closing operation is then performed by smoothing to ensure that the local curvature at all points on the smoothed pial surface (the“hull” surface) is less than the curvature of a 15-mm radius sphere. The chosen radius of 15 mm for the closing operation ensures that the hull surface does not dip into the sulci and remains tight but external to the sulcal dips. This hull surface acts as the outer perimeter, whereas original pial surface provides the inner perimeter. Both inner and outer surfaces are tessellated with numerous vertices that are formed by the meeting points of triangles. For each vertex (j) on the outer surface, a spherical region of interest is created with the vertex as the centre point and a standard 25-mm radius. This sphere yields two area measures for each vertex. The outer measure (Area jO) is area of that part of the hull defined by the intersection of this sphere with the hull surface. To measure the corresponding pial surface area, the respective pial region of interest for the given vertex on outer hull surface is determined as follows. Initially all vertices within Area jO (on the hull surface) are identified. After this, the nearest pial vertex to each of these hull vertices is identified. These pial vertices define the outline of pial mesh, whose area is then calculated with sum of areas of all included triangular tessellations (Area jP).

The ratio of the pial surface area to the outer surface area gives the LGI for each vertex on the outer surface (Area j P/AreajO). These outer surface values are redistributed to the pial surface with a weighted sum of all outer surface LGIs to which each pial vertex contributed during the prior computation. The weighting was inversely proportional to the distance of the hull vertex from the pial vertex. Thus, the LGI for each vertex on pial surface reflects the amount of cortex buried in its locality. The mean LGI calculated with all vertices present within a predefined sulco-gyral region of the atlas is used as the LGI of that anatomical subregion. Thus, three LGI values (global, temporal and frontal) were obtained for each hemisphere (as obligated by the software) and participant for further analysis.

***Results***

**Table S1 –** Group differences in polygenic risk scores and mean PGRS-SCZ per group shown at all 5 thresholds

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  |  | *HC (n=16)* | *HR[well] (n=31)* | *HR[symp] (n=28)* | *HR[ill] (n=9)* |
|  | **F** | **p** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |
| **p≤0.01** | 2.69 | 0.053**\*** | -0.56 (1.16) | -0.09 (0.81) | 0.27 (1.06) | 0.47 (0.70) |
| **p≤0.05** | 2.90 | 0.040**\*** | -0.57 (1.07) | -0.07 (0.77) | 0.22 (1.12) | 0.56 (0.78) |
| **p≤0.1** | 2.91 | 0.040**\*** | **-0.54 (1.05)** | **-0.07 (0.79)** | **0.18 (1.10)** | **0.63 (0.87)** |
| **p≤0.5** | 2.91 | 0.040**\*** | -0.53 (0.94) | -0.10 (0.76) | 0.22 (1.16) | 0.59 (0.94) |
| **p≤1** | 3.20 | 0.028**\*** | -0.56 (0.92) | -0.09 (0.75) | 0.22 (1.16) | 0.60 (0.95) |

\*p≤0.05

**Table S2** – Pairwise comparisons (Tukey) for the main effect of group on polygenic risk score using the ANCOVA models

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Estimate** | **Standard Error** | **padjusted** |
| HC vs HR[well] | -0.56 | 0.31 | 0.277 |
| HC vs HR[symp] | -0.69 | 0.32 | 0.152 |
| **HC vs HR[ill]** | **-1.18** | **0.43** | **0.037\*** |
| HR[well] vs HR[symp] | -0.13 | 0.27 | 0.963 |
| HR[well] vs HR[ill] | -0.62 | 0.40 | 0.407 |
| HR[symp] vs HR[ill] | -0.49 | 0.42 | 0.641 |

\*p≤0.05

**Table S3 –** Effect of polygenic risk score for schizophrenia on temporal and frontal gyrification. FDR corrected for lobar analyses.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***p* ≤ 0.01** | | ***p* ≤ 0.05** | | ***p* ≤ 0.1** | | ***p* ≤ 0.5** | | ***p* ≤ 1** | |
| F | *p*  (*p*corrected) | F | *p* (*p*corrected) | F | *p*  (*p*corrected) | F | *p* (*p*corrected) | F | *p* (*p*corrected) |
| *High Risk (n = 68)* |  |  |  |  |  |  |  |  |  |  |
| **Frontal L** | 4.32 | 0.042\* (0.138) | 6.00 | 0.017\* (0.068**.**) | 7.37 | 0.010\*\* (0.040**\***) | 7.82 | 0.007\*\* (0.028**\***) | 7.48 | 0.008\*\* (0.032**\***) |
| **Frontal R** | 3.44 | 0.069**.** (0.138) | 3.99 | 0.050\* (0.100) | 5.38 | 0.024\* (0.048**\***) | 4.10 | 0.048\* (0.096**.**) | 4.46 | 0.039\* (0.078**.**) |
| **Temporal L** | 0.03 | 0.875 (0.875) | 0.06 | 0.814 (0.814) | 0.00 | 1.000 (1.000) | 0.04 | 0.845 (0.998) | 0.17 | 0.681 (0.880) |
| **Temporal R** | 0.09 | 0.768  (0.875) | 0.14 | 0.710 (0.814) | 0.00 | 0.951) (1.000) | 0.00 | 0.998 (0.998) | 0.02 | 0.880 (0.880) |
| *Controls*  *(n = 16)* |  |  |  |  |  |  |  |  |  |  |
| **Frontal L** | 0.30 | 0.599 | 0.84 | 0.390 | 0.38 | 0.566 | 0.55 | 0.481 | 0.53 | 0.492 |
| **Frontal R** | 1.03 | 0.345 | 1.30 | 0.292 | 0.41 | 0.542 | 0.38 | 0.555 | 0.30 | 0.602 |
| **Temporal L** | 0.79 | 0.403 | 1.23 | 0.304 | 1.80 | 0.222 | 1.38 | 0.279 | 1.37 | 0.281 |
| **Temporal R** | 0.15 | 0.715 | 0.08 | 0.780 | 0.00 | 0.966 | 0.01 | 0.924 | 0.00 | 0.100 |

\*\*\*p≤0.001

\*\*p≤0.01

\*p≤0.05

**.** p≤0.10

**Table S4** - Results for analysis of associations between gyrification and polygenic risk scores within the high-risk sub-groups at all 5 thresholds. FDR corrected for test sub-groups.

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | ***p* ≤ 0.01** | | ***p* ≤ 0.05** | | ***p* ≤ 0.1** | | ***p* ≤ 0.5** | | ***p* ≤ 1** | |
| F | *p*  (*p*corrected) | F | *p* (*p*corrected) | F | *p*  (*p*corrected) | F | *p*  (*p*corrected) | F | *p* (*p*corrected) |
| *HR[well]*  *(n = 31)* |  |  |  |  |  |  |  |  |  |  |
| **Frontal L** | 0.74 | 0.398 (0.398) | 0.54 | 0.470 (0.560) | 0.36 | 0.383 (0.383) | 0.35 | 0.562 (0.562) | 0.30 | 0.592 (0.592) |
| **Frontal R** | 0.00 | 0.971 (0.971) | 0.00 | 0.960 (0.960) | 0.05 | 0.817 (0.817) | 0.03 | 0.858 (0.858) | 0.04 | 0.845 (0.845) |
| *HR[symp]*  *(n = 28)* |  |  |  |  |  |  |  |  |  |  |
| **Frontal L** | 3.13 | 0.092**.**  (0.276) | 4.60 | 0.045**\*** (0.135) | 6.21 | 0.022 (0.065) | 7.22 | 0.014**\*\*** (0.042**.**) | 6.71 | 0.017**\*** (0.051**\***) |
| **Frontal R** | 5.78 | 0.030**\*** (0.090**.**) | 8.12 | 0.010**\*\*** (0.030**\***) | 10.63 | 0.004**\*\*** (0.012**\*\***) | 8.91 | 0.007**\*\*** (0.021**\***) | 9.10 | 0.007**\*\*** (0.021**\***) |
| *HR[ill]*  *(n = 9)* |  |  |  |  |  |  |  |  |  |  |
| **Frontal L** | 7.03 | 0.230 (0.345) | 0.54 | 0.560 (0.560) | 2.12 | 0.383 (0.383) | 1.16 | 0.477 (0.562) | 1.71 | 0.415 (0.592) |
| **Frontal R** | 56.23 | 0.084 (0.126) | 3.69 | 0.306 (0.459) | 57.12 | 0.084**.** (0.126) | 13.19 | 0.171  (0.257) | 32.62 | 0.110 (0.165) |

\*\*\*p≤0.001

\*\*p≤0.01

\*p≤0.05

**.** p≤0.10

**Table S5** – Group differences in mean gyrification for all regions of interest

|  |  |  |
| --- | --- | --- |
|  | **F** | ***p*** |
| **Left Frontal** | 0.56 | 0.643 |
| **Right Frontal** | 0.59 | 0.623 |
| **Left Temporal** | 0.63 | 0.600 |
| **Right Temporal** | 1.47 | 0.229 |

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