**SUPPLEMENTAL MATERIAL**

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**Appendix 1: Image acquisition and Freesurfer processing**

**Image acquisition:** Magnetic resonance scans were collected using 2 Philips 3-T imaging systems (located in the University of Nottingham) equipped with 8-channel phased array head coil with identical acquisition parameters. Images from 143 subjects were acquired from one scanner, while 38 (18 patients and 20 controls) were acquired from the other in the course of 2 distinct neuroimaging studies. The scanning protocol included a single high-resolution three-dimensional T1-weighted MPRAGE volume of isotropic voxel size 1 × 1 × 1 mm3, flip angle 8°, field of view 256 × 256 × 160 mm3. 160 slices of 1mm thickness each were collected in an acquisition matrix 256 mm × 256 mm and in-plane resolution 1 × 1mm2.

Surface extraction and cortical parcellation were carried out using FreeSurfer version 4.5.0. The preprocessing was carried out according to the description available at (http://surfer.nmr.mgh.harvard.edu/). Briefly, following skull-stripping and intensity correction, the grey–white matter boundary for each cortical hemisphere was determined using tissue intensity and neighborhood constraints. The resulting surface boundary was tessellated to generate multiple vertices across the whole brain before inflating. Using a deformable surface algorithm guided by the grey-CSF intensity gradient, the resulting grey-white interface was expanded to create the pial surface. The inflated surface was then morphed into a sphere followed by registration to an average spherical surface for optimal sulcogyral alignment.

**Exclusion criteria for motion artifacts in MPRAGE acquisition**

Scans with at least 1 of the following 3 criteria were excluded owing to motion artifacts:

1. Images too grainy: grey–white matter boundary is clearly invisible in more than 2 anatomically distinct regions
2. Significant edge ringing artifacts: more than 2 rings noted with associated blurring of grey–white matter boundary in more than 2 anatomically distinct regions
3. Less severe motion artifacts/grainy image but not satisfying criteria 1 and 2, but either

* fails Freesurfer cortical reconstruction owing to substantial topological defects; or
* presence of more than 2 handles/holes that require manual intervention (e.g. hole-filling, defining control points, removal of obscure/uncertain pia-like tissue) to define grey–white matter boundaries despite Freesurfer’s automatic topological fixation procedure

MPRAGE = magnetization-prepared rapid-acquisition gradient echo. From Palaniyappan L, Liddle P.F. Aberrant cortical gyrification in schizophrenia: a surface-based morphometry study. J Psychiatry Neurosci 2012.

**Destrieux Atlas**

DestrieuxAtlas is based on a parcellation scheme that first divides the cortex into gyral and sulcal regions based on the surface curvature values. A gyrus only includes the cortex visible on the pial view, the hidden cortex (banks of sulci) are marked sulcus. There are 148 separate parcellations in total, the detailed description of these parcellations are shown in Table S1 and Figure S1. We chose Destrieux atlas over the other commonly used Freesurfer atlas as we anticipated that compensatory structural changes in schizophrenia would involve fine-grained regional changes that may not be appreciable when mean values over a larger scale are considered, as would be the case when using lobar parcellations or Desikan’s combined sulcogyral units.

**Table S1: List of anatomical parcellations.**

|  |  |  |
| --- | --- | --- |
| **Index** | **Short name** | **Long name** |
| 1, 75 | anterior cingulate | Anterior part of the cingulate gyrus and sulcus |
| **2, 76** | middle-anterior cingulate | Middle-anterior part of the cingulate gyrus and sulcus |
| **3,77** | middle-posterior cigulate | Middle-posterior part of the cingulate gyrus and sulcus |
| **4,78** | frontomargin | Fronto-marginal gyrus (of Wernicke) and sulcus |
| **5,79** | Inferior occipital | Inferior occipital gyrus (O3) and sulcus |
| **6,80** | paracentral | Paracentral lobule and sulcus |
| **7,81** | subcentral | Subcentralgyrus (central operculum) and sulci |
| **8,82** | transversefrontpolar | Transverse frontopolargyri and sulci |
| **9, 83** | posterior-dorsal cingulate | Posterior-dorsal part of the cingulate gyrus |
| **10, 84** | posterior-ventral cingulate | Posterior-ventral part of the cingulate gyrus |
| **11, 85** | cuneus | Cuneus |
| **12, 86** | inferioropercular | Opercular part of the inferior frontal gyrus |
| **13, 87** | inferior orbital | Orbital part of the inferior frontal gyrus |
| **14, 88** | Inferior triangular | Triangular part of the inferior frontal gyrus |
| **15, 89** | middle frontal | Middle frontal gyrus |
| **16, 90** | superiorfrontal | Superior frontal gyrus |
| **17, 91** | longinsula | Long insular gyrus and central sulcus of the insula |
| **18, 92** | shortinsula | Short insular gyri |
| **19, 93** | middleoccipital | Middle occipital gyrus |
| **20, 94** | superioroccipital | Superior occipital gyrus |
| **21, 95** | lateralfusiform | Lateral occipito-temporal gyrus |
| **22, 96** | medial lingual | Lingual gyrus, lingual part of the medial occipito-temporal gyrus |
| **23, 97** | parahippocampal | parahippocampal part of the medial occipito-temporal gyrus |
| **24, 98** | orbital | Orbital gyri |
| **25, 99** | angular | Angular gyrus |
| **26, 100** | supramarginal | Supramarginalgyrus |
| **27, 101** | superior parietal | Superior parietal lobule |
| **28, 102** | postcentral | Postcentralgyrus |
| **29, 103** | precentral | Precentral gyrus |
| **30, 104** | precuneus | Precuneus |
| **31, 105** | rectus | Straight gyrus, Gyrus rectus |
| **32, 106** | subcallosal | Subcallosal area, subcallosalgyrus |
| **33, 107** | anterior transverse | Anterior transverse temporal gyrus |
| **34, 108** | lateral temporal | Lateral aspect of the superior temporal gyrus |
| **35, 109** | temporalpolar | Planumpolare of the superior temporal gyrus |
| **36, 110** | temporalplanum | Planumtemporale or temporal plane of the superior temporal gyrus |
| **37, 111** | temporal | temporalgyrus |
| **38, 112** | middletemporal | Middle temporal gyrus |
| **39, 113** | horizontal | Horizontal ramus of the anterior segment of the lateral sulcus |
| **40, 114** | vertical | Vertical ramus of the anterior segment of the lateral sulcus |
| **41, 115** | lateral fissure | Posterior ramus (or segment) of the lateral sulcus (or fissure) |
| **42, 116** | occipital pole | Occipital pole |
| **43, 117** | temporal pole | Temporal pole |
| **44, 118** | calcarine | Calcarine sulcus |
| **45, 119** | central | Central sulcus |
| **46, 120** | cingulated marginal | Marginal branch (or part) of the cingulate sulcus |
| **47, 121** | anteriorinsula | Anterior segment of the circular sulcus of the insula |
| **48, 122** | inferior insula | Inferior segment of the circular sulcus of the insula |
| **49, 123** | superior insula | Superior segment of the circular sulcus of the insula |
| **50, 124** | anteriortransverse | Anterior transverse collateral sulcus |
| **51, 125** | posteriortransverse | Posterior transverse collateral sulcus |
| **52, 126** | inferior frontal | Inferior frontal sulcus |
| **53, 127** | middle frontal | Middle frontal sulcus |
| **54, 128** | superior frontal | Superior frontal sulcus |
| **55, 129** | intermedius | Sulcus intermedius primus (of Jensen) |
| **56, 130** | intraparietal | Intraparietal sulcus (interparietal sulcus) and transverse parietal sulci |
| **57, 131** | middle occipital | Middle occipital sulcus and lunatus sulcus |
| **58, 132** | superior occipital | Superior occipital sulcus and transverse occipital sulcus |
| **59, 133** | anterioroccipital | Anterior occipital sulcus and preoccipital notch (temporo-occipital incisure) |
| **60, 134** | lateral occipital | Lateral occipito-temporal sulcus |
| **61, 135** | medial occipital | Medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus |
| **62, 136** | lateral orbital | Lateral orbital sulcus |
| **63, 137** | medial orbital | Medial orbital sulcus (olfactory sulcus) |
| **64, 138** | orbital | Orbital sulci (H-shaped sulci) |
| **65, 139** | parietooccipital | Parieto-occipital sulcus (or fissure) |
| **66, 140** | pericallosal | Pericallosal sulcus (S of corpus callosum) |
| **67, 141** | postcentral | Postcentral sulcus |
| **68, 142** | inferiorprecentral | Inferior part of the precentral sulcus |
| **69, 143** | superiorprecentral | Superior part of the precentral sulcus |
| **70, 144** | suborbital | Suborbital sulcus (sulcus rostrales, supraorbital sulcus) |
| **71, 145** | subparietal | Subparietal sulcus |
| **72, 146** | inferior temporal | Inferior temporal sulcus |
| **73, 147** | superior temporal | Superior temporal sulcus (parallel sulcus) |
| **74, 148** | transverse temporal | Transverse temporal sulcus |

Note: number 1-74 represent left hemisphere, number 75-148 represent right hemisphere.



**Figure S1:**Pial view of the manual parcellation of one hemisphere of the Destrieux atlas. Numerical indices refer to the anatomical regions defined in Table S1: superior (Sup), anterior (Ant), lateral (Lat), posterior (Post), medial (Med), and inferior views are provided.

**Table S2: Correlation between adjusted regional thickness and illness duration.**

|  |  |  |  |
| --- | --- | --- | --- |
| ROI | Status of thickness in patients when compared to controls (group comparison) | Correlation coefficients | Uncorrected P value |
| lh- inferior occipital | Increased thickness | -0.4396 | 0.0000 |
| rh-lateral fissure | Increased thickness | -0.4293 | 0.0000 |
| lh-inferior occipital | Increased thickness | -0.4136 | 0.0000 |
| rh-calcarine | Increased thickness | -0.3526 | 0.0004 |
| lh-occipital pole | Increased thickness | -0.3409 | 0.0006 |
| lh- lateral fissure | Increased thickness | -0.3352 | 0.0007 |
| lh-calcarine | Increased thickness | -0.3271 | 0.0010 |
| rh-occipital pole | Increased thickness | -0.2959 | 0.0031 |
| lh-temporal pole | Decreased thickness | 0.4338 | 0.0000 |
| lh-supramarginal | Decreased thickness | 0.4014 | 0.0000 |
| lh-precentral | Decreased thickness | 0.4010 | 0.0000 |
| rh-parahippocampal | Decreased thickness | 0.3975 | 0.0001 |
| lh-parahippocampal | Decreased thickness | 0.3770 | 0.0001 |
| rh-supramarginal | Decreased thickness | 0.3515 | 0.0004 |
| rh-precentral | Decreased thickness | 0.3213 | 0.0013 |
| rh-temporal pole | Decreased thickness | 0.3197 | 0.0013 |
| lh-rectus | Decreased thickness | 0.2666 | 0.0080 |
| rh-superior parietal | Decreased thickness | 0.2465 | 0.0144 |
| rh-frontomarginal | Decreased thickness | 0.2363 | 0.0191 |

**Covariance Analysis**

We obtained the inter-regional correlation matrix,  for each group by calculating Pearson’s correlation coefficients across subjects between the residual cortical thicknesses of every pair of regions. That was:



Where  was the vector of residual cortical thickness of parcellation across all subjects,  was the number of subjects,  was the mean residual cortical thickness of parcellation ,  was the normalized covariant coefficient of parcellationand for subject . represented the changes of thickness between parcellation and were convergent (i.e., in the same direction of increasing or decreasing together),  represented the changes of thickness between parcellation and  were divergent (i.e., in the opposite direction of increasing or decreasing together). The covariance analysis included all possible regional pairs.

**Predictors in different bins of illness duration**

We report in the main text how taking illness duration into consideration could remarkably improve the accuracy of discriminating patients and controls using SVM. For the different (exclusive) illness duration bins, the best predictors were also different. In order to obtain the best predictors for each bin between patients and controls, we randomly select the age-matched controls and get the top 5 best predictors every time. We repeat such procedure for 1000 times and select the top 5 predictor with the highest frequency. Table S3 displays the top 5 best predictors in each bin.

**Table S3 : Best Predictors in each bin.**

|  |  |
| --- | --- |
| Duration | Top 5 Best predictors |
| <2(25 patients vs 83 control) | lh-parahippocampal  rh-parahippocampal  lh-supramarginal  lh-temporal pole  rh-lateral fissure |
| 2<D<4(27 patients vs 83 control) | rh-transverse temporal  rh-inferior precentral  rh-temporal pole  lh-inferior temporal  rh-orbital |
| 4<D<10(26 patients vs 83 control) | rh-intraparietal  lh-subcallosal  rh-temporal pole  rh-subcallosal  lh-inferior precentral |
| D>10(20 patients vs 83 control) | rh-medial cingulate  rh-superior insula  lh-middle temporal  rh-medial cingulate  rh\_ anterior transverse |
| Alldata(98 patients vs. 83 controls) | lh\_parahippocampal  lh\_supramarginal  lh\_precentral  lh\_temporal pole  rh\_parahippocampal |

**Table S4: Significant negative links of structure cortical network among the top 100 significant links in each group.**

|  |  |
| --- | --- |
| **Links** | **Correlation coefficients** |
| **controls** | |
| lh-superior frontal------rh-intraparietal | -0.6136 |
| **Patients with schizophrenia** | |
| lh- Inferior occipital-----lh-parahippocampal | -0.6807 |
| lh- Inferior occipital ---- lh-supramarginal | -0.8448 |
| lh- Inferior occipital ----lh-precentral | -0.6525 |
| lh- Inferior occipital ----rh-parahippocampal | -0.7583 |
| lh- Inferior occipital----rh-supramarginal | -0.7664 |
| lh- Inferior occipital ----rh-superior parietal | -0.7200 |
| lh-parahippocampal ----lh-occipital pole | -0.6664 |
| rh- Inferior occipital -----lh-parahippocampal | -0.6651 |
| lh-parahippocampal----rh- lateral fissure | -0.6603 |
| lh-parahippocampal----rh- occipital pole | -0.6764 |
| lh-parahippocampal----rh- calcarine | -0.7297 |
| lh-supramarginal----lh- lateral fissure | -0.7507 |
| lh-supramarginal----lh- occipital pole | -0.6850 |
| lh-supramarginal----rh- Inferior occipital | -0.8079 |
| lh-supramarginal----rh- lateral fissure | -0.7882 |
| lh-supramarginal----rh- occipital pole | -0.7347 |
| lh-supramarginal----rh-calcarine | -0.8253 |
| lh-precentral---- rh- Inferior occipital | -0.6559 |
| lh-precentral---- rh- lateral fissure | -0.6646 |
| lh-precentral---- rh-calcarine | -0.6571 |
| lh- lateral fissure----rh- parahippocampal | -0.7150 |
| lh- lateral fissure----rh- supramarginal | -0.6485 |
| lh- occipital pole---- rh- parahippocampal | -0.6786 |
| lh- occipital pole-----rh- supramarginal | -0.6788 |
| lh-calcarine---- rh- supramarginal | -0.6838 |
| lh-Inferior occipital---- rh- parahippocampal | -0.7636 |
| lh-Inferior occipital---- rh- supramarginal | -0.7650 |
| lh-Inferior occipital----rh- superior parietal | -0.6855 |
| rh- parahippocampal----rh- lateral fissure | -0.7393 |
| rh- parahippocampal----rh- occipital pole | -0.6957 |
| rh- parahippocampal----rh- calcarine | -0.7808 |
| rh- supramarginal---- rh- lateral fissure | -0.7576 |
| rh- supramarginal---- rh- occipital pole | -0.6772 |
| rh- supramarinal---- rh- calcarine | -0.8200 |
| rh- superior parietal---- rh- lateral fissure | -0.6840 |
| rh- superior parietal---- rh- calcarine | -0.7123 |

**Table S5: Structural covariance of regions with significant difference in thickness.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| regions | t-statistics  (C-P) | P value | #Significant links(C/P) | Percentage of negative links(C/P) |
| lh-parahippocampal | 9.7549 | 0 | 4/24 | 0/37.5% |
| lh-supramarginal | 9.9492 | 0 | 33/30 | 0/33.33% |
| lh-precentral | 9.5513 | 0 | 15/22 | 0/36.36% |
| lh-temporal pole | 10.2196 | 0 | 4/35 | 0/22.86% |
| rh-parahippocampal | 11.0280 | 0 | 4/24 | 0/37.5% |
| rh-supramarginal | 9.9248 | 0 | 33/29 | 0/34.48% |
| rh-temporal pole | 9.9322 | 0 | 5/34 | 0/23.53% |
| rh-precentral | 9.1846 | 1.1\*10-16 | 32/23 | 0/39.13% |
| rh-superior insula | 8.6769 | 2.4\*10-15 | 2/30 | 0/23.33% |
| rh-inferior occipital | -7.165 | 1.9\*10-11 | 4/28 | 0/53.57% |
| lh-inferior occipital | -6.74 | 2.0\*10-10 | 6/29 | 0/55.17% |
| lh-lateral fissure | -6.56 | 5.4\*10-10 | 8/24 | 0/50% |
| rh-calcarine | -6.49 | 8.3\*10-10 | 7/27 | 0/48.15% |
| rh-lateral fissure | -6.38 | 1.4\*10-9 | 6/25 | 0/56% |
| lh-occipital pole | -6.32 | 1.9\*10-9 | 9/23 | 0/52.17% |
| rh-occipital pole | -6.16 | 4.2\*10-9 | 1/22 | 0/45.45% |
| lh-calcarine | -5.48 | 1.4\*10-7 | 9/24 | 0/45.83% |

Note: C: control; P: patients with schizophrenia

**Table S6: Demographic comparison of two groups with different illness duration.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Duration bin | # patients | # controls | P value of age | P value of gender |
| <30 | 98 | 83 | 0.4910 | 0.6303 |
| <25 | 97 | 83 | 0.5804 | 0.6106 |
| <20 | 92 | 83 | 0.7687 | 0.8589 |
| <15 | 87 | 83 | 0.1009 | 0.9191 |
| <10 | 78 | 83 | 0.0456 | 0.8356 |
| <7 | 74 | 83 | 0.0416 | 0.7505 |
| <6 | 70 | 83 | 0.0190 | 0.8067 |
| <5 | 61 | 83 | 0.0081 | 0.9067 |
| <4 | 52 | 83 | 0.0031 | 0.9657 |
| <3 | 42 | 83 | 0.0058 | 0.6358 |
| <2 | 25 | 83 | 0.0017 | 0.6139 |

**illnessvsage.tif**

**Figure S2: (A)** Distribution of illness duration of all 98 subjects. (B) Mean age of patients with different illness duration.

**Table S7: SVM results after removing the differential effect of the 2 scanners.**

To study the effect of the 2 scanners on the variations in discrimination accuracy, we recalculated the duration-specific SVM accuracy after removing the effect of scanner using a dummy-coded linear regression. The results are presented in the following Table S8. The same pattern of reducing classification accuracy with increasing duration is replicated.

|  |  |  |  |
| --- | --- | --- | --- |
| duration | Accuracy | Specificity | Sensitivity |
| All data(98 patients vs 83 control) | 83.43% | 91.57% | 76.53% |
| <25(97 patients vs 83 control) | 83.89% | 92.77% | 76.29% |
| <20(92 patients vs 83 control) | 85.14% | 92.77% | 78.26% |
| <15(87 patients vs 83 control) | 85.88% | 95.18% | 77.01% |
| <10(78 patients vs 83 control) | 86.96% | 97.59% | 75.64% |
| <7(74 patients vs 83 control) | 88.54% | 97.59% | 78.38% |
| <6(70 patients vs 83 control) | 89.54% | 97.59% | 80% |
| <5(61 patients vs 83 control) | 90.97% | 97.59% | 81.97% |
| <4(52 patients vs 83 control) | 91.85% | 97.59% | 82.69% |
| <3(42 patients vs 83 control) | 94.4% | 98.8% | 85.71% |
| <2(25 patients vs 83 control) | 96.3% | 98.8% | 88% |

**Table S8: Effect of sample size differences**

To study the effect of sample imbalance on the variations in discrimination accuracy, we recalculated the duration-specific SVM accuracy for exclusive duration bins by balancing the sample size. For this analysis, we selected the same sample size of controls as that of patients, with each patient matched with the control for nearest age, followed by 1000-fold cross-validation. The results are presented in the following Table S8. The same pattern of reducing classification accuracy with increasing duration is replicated.

|  |  |  |  |
| --- | --- | --- | --- |
| Exclusive duration bins | | | |
| D<2(25 patients vs 25 age-matched controls) | 93.6% | 96.56% | 90.64% |
| 2<D<4(27 patients vs 27 age-matched controls) | 87.35% | 96.37% | 78.33% |
| 4<D<10(26 patients vs 26 age-matched controls) | 75.56% | 84.08% | 67.04% |

D: Duration of illness in years. For the bin with D>10, an nearest age-matched control sample of similar size (20) was not available, as we had fewer controls than patients in this study.

dose.tif

Figure S3: (A) Correlation matrices constructed from thickness measure after removing the effect of current chlorpromazine equivalent antipsychotic dose. The lower triangular matrix represents the correlation coefficients of patients and the upper triangular matrix represented the correlation coefficients of controls. (B) The percentage of the divergent pairwise relationships for different correlation thresholds in the two groups. (C) The error bar of normalized covariant coefficients for the top 100 significant links in each group. The red line represented mean normalized covariant coefficients of each link. Controls are in the upper row, patients in the lower row.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Exclusive duration bins | antipsychotic dose | total SSPI score | psychomotor poverty | reality distortion | disorganisation |
| <2(mean/std) | 364.3(372) | 9.2(5.2) | 3.2(3.34) | 2.08(2.4) | 0.88(1.09) |
| 2<D<4(mean/std) | 400(267) | 10.6(7.3) | 2.3(2.58) | 2.67(2.6) | 0.92(1.2) |
| 4<D<10(mean(std) | 309(264) | 11.1(7.1) | 3.5(3.53) | 1.92(2.1) | 0.92(1.09) |
| D>10(mean/std) | 572(370) | 13.2(7.6) | 2.4(3.07) | 3.25(2.6) | 1.3(1.5) |
| Test(F/p value) | 2.46(0.068) | 1.28(0.29) | 0.88(0.452) | 1.4(0.24) | 0.55(0.65) |

**Figure S4: Colour version of Figure 4 from the published manuscript**

Figure S4: Hub-and-spoke representation of the covariance between regions with significant group difference and rest of the brain. The central node represents the region with significant increase (occipital) or decrease (parahippocampal and supramarginal) in thickness. The outer nodes represent all brain regions that have a significant covariance with the central node either in the patient group or the control group. Regions with increased thickness (green) and decreased thickness (yellow) are separately identified from those that show no significant group differences in thickness (grey). The spokes represent the relationship between the central and outer nodes. Red spokes represent negative (divergence of covariance) relationships while blue spokes represent positive (convergence of covariance) relationships. The numbers shown in the figure correspond to specific brain regions as listed in Supplementary Table S1.

