**SUPPLEMENTARY MATERIAL**

**Neuregulin-1 (*NRG1*) polymorphisms linked with psychosis onset are associated with enlarged lateral ventricles and white matter disruption in schizophrenia**

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**Supplementary methods**

**DNA extraction and genotyping**

gDNA was extracted from 1 to 10 ml of whole blood collected in EDTA tubes using a commercially available QIAamp DNA Blood Midi or Maxi Kit (QIAGEN) according to the manufacturer’s protocol. Briefly samples were lyzed, the lysate loaded onto a QIAamp spin column and impurities washed away from bound DNA in two centrifugation steps. Purified DNA was then eluted from the column following repeated centrifugation at 4500 x *g* for 5 mins at room temperature. DNA was diluted to 0.1 µg/µl in DNase free water and stored at −80oC until utilized.

Purified gDNA was genotyped for NRG1 SNPs rs4281084 and rs12155594*.* PCR primers were:

rs4281084: Forward 5′-ACGTTGGATGCTCTCTACCTTCCAGATTTG-3′ and reverse 5′-ACGTTGGATGGGGCTAAATGAACCAACAGG-3′

rs12155594: forward 5′-ACGTTGGATGTGTACTATCCTCTGTCATGG-3′ and reverse 5′-ACGTTGGATGGCATTATACAATACAATGCAG-3′

Oligonucleotides contained 10-mer 5’ tags and were designed to amplify 107 and 101 base pair amplicons, respectively. Briefly, amplification was performed using 5 to 10 ng of gDNA, 4.0 mM MgCl2, 500 uM dNTPs, 100 nM primer mix and 0.5 U Taq polymerase in a standard thermal cycler. PCR conditions comprised a 15 min pre-incubation at 95°C followed by 45 cycles at 94oC for 20 secs; 56oC for 30 secs; 72oC for 1 min and a final extension at 72oC for 3 mins. iPLEX Gold reaction chemistry and multiplex Sequenom MassArray technology was then applied to obtain sequence data at the Australian Genome Research Facility (AGRF, Brisbane, Australia). Genotyping was repeated on a random 10% subset of samples with 100% reliability for all calls.

**Magnetic resonance imaging acquisition parameters**

*T1-weighted images*

Structural (T1-weighted) imaging of brain anatomy was performed in each participant with a Siemens Avanto 1.5-Tesla system (Siemens, Erlangen, Germany) at one of five sites in Australia: Melbourne, Sydney, Perth, Newcastle and Brisbane. T1-weighted images comprised 176 sagittal slices/brain of 1mm thickness without gap; field of view = 250 x 250 mm2; repetition time/echo time = 1980/4.3 ms; data matrix size = 256 x 256; voxel dimensions = 1.0 x 1.0 x 1.0 mm3. Images were processed using a modified version of FreeSurfer 5.1.0 software (<http://surfer.nmr.mgh.harvard.edu/>) obtained directly from the Freesurfer developers, Bruce Fischl and Nick Schmansky. This was necessary to ameliorate the “mris\_make\_surfaces bug”, which confounded surface reconstruction after manual editing. Note that this modification was subsequently implemented in FreeSurfer 5.3.0 (see Freesurfer release notes, [http://surfer.nmr.mgh.harvard.edu/fswiki/ReleaseNotes](https://owa.unimelb.edu.au/OWA/redir.aspx?C=RvQsK0oUpUqzZtYp5Ms1eKH0kN-YWs8IG158J99wtcuBPy3v3ooMY2jTatnovwum6UiovQ2t8SI.&URL=http%3a%2f%2fsurfer.nmr.mgh.harvard.edu%2ffswiki%2fReleaseNotes" \t "_blank)). The Freesurfer pipeline consists of a volume-based and a surface-based stream. The automated volume-based stream was performed to extract volume estimates (i.e. for the lateral ventricle). This procedure assigns a neuroanatomical label to each voxel in a MRI volume using a probabilistic atlas and a Bayesian classification rule([Fischl et al., 2002](#_ENREF_7)). The surface-based cortical reconstruction stream was performed to derive the white and pial surfaces, from which the Freesurfer measures, cortical thickness, surface area and cortical volumes, are derived ([Dale et al., 1999](#_ENREF_4); [Fischl et al., 2002](#_ENREF_7); [Fischl et al., 1999](#_ENREF_8); [Fischl et al., 2004](#_ENREF_9)). All images were visually inspected to verify the accuracy of reconstructions and identify errors, including skull-strip errors, gross segmentation errors and white/gray matter and pial surface inaccuracies. Surface inaccuracies were manually corrected with Freesurfer’s editing tools in accordance with an internal, standardized quality control and editing protocol. Edited images were then reprocessed through the Freesurfer pipeline and the output visually inspected again. This process was repeated until all surface errors were corrected, and any images that failed this process were excluded from analysis. Thickness, surface area and volume (cortical and subcortical) estimates were obtained using the Desikan-Killiany brain atlas from successfully processed MRI volumes. Four trained raters performed the Freesurfer processing and manual correction, blind to participant diagnosis. Inter-rater reliability of the final volume estimates (after correction) was calculated for 32 brain regions from a subset of 20 volumes. The intra-class coefficient (ICC) was >.90 for all regions except for the left (0.72) and right (0.59) temporal pole and the left (0.81) and right (0.82) frontal pole.

*Diffusion weighted images*

Diffusion magnetic resonance imaging of brain anatomy was performed in each participant with a Siemens Avanto 1.5-Tesla system (Siemens, Erlangen, Germany) at one of five sites in Australia: Melbourne, Sydney, Perth, Newcastle and Brisbane. Diffusion images comprised 64 gradient-weighted volumes acquired using a spin-echo EPI sequence with: b-value, 1000 s/mm2; 65 consecutive axial slices of thickness 2.4 mm; 104×104 image matrix with an in-plane voxel resolution of 2.4×2.4 mm; field of view, 25×25 cm; repetition time, 8.4/8.5 s; echo time, 88 ms; flip angle, 90 degrees.

The diffusion images were corrected for distortions and head movement with affine registration. The gradient tables were modified accordingly. The corrected images were normalized to MNI standard space using the non-linear registration tools provided as part of FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/). The registration target was the FMRIB58\_FA template provided with FSL package (an average of 58 well-aligned good quality FA images). Images were manually examined for registration artifacts. To improve the signal to noise ratio, images were finally smoothed with a Gaussian kernel width of 1 mm.

**Ethics**

Ethics approval for the data collection portion of the ASRB study was provided by HNEHREC 08/12/17/5.20, HREC/08/HNE/438, SSA/09/HNE/23 and all participants provided informed consent. Approval to analyse the de-identified ASRB dataset was provided by the Melbourne Health Human Research Ethics Committee (MHREC: 2010.250).

**Supplementary Table S1:** Minor allele frequencies (MAF) for rs4281084 and rs12155594 within the ASRB and the 27 populations included in the 1000 Genomes Project (Phase 3, May 2013 call set). p values are based on a two-sample z-test.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  |  | **rs4281084 (A)** | |  | **rs12155594 (T)** | |
| **Population** | **N** | **MAF** | **p** |  | **MAF** | **p** |
| Study Cohort |  |  |  |  |  |  |
| Australian Schizophrenia Research Bank (ASRB) | 333 | 0.244 | n/a |  | 0.120 | n/a |
| European |  |  |  |  |  |  |
| British in England and Scotland (GBR) | 94 | 0.308 | 0.480 |  | 0.115 | 0.683 |
| Finnish in Finland (FIN) | 100 | 0.227 | 0.649 |  | 0.131 | 0.545 |
| Iberian populations in Spain (IBS) | 107 | 0.243 | 0.760 |  | 0.098 | 0.999 |
| Toscani in Italia (TSI) | 110 | 0.266 | 0.881 |  | 0.126 | 0.538 |
| Utah residents with Northern and Western European ancestry (CEU) | 103 | 0.212 | 0.439 |  | 0.116 | 0.678 |
| East Asian |  |  |  |  |  |  |
| Chinese Dai in Xishuangbanna, China (CDX) | 99 | 0.253 | 0.882 |  | 0.000 | 0.002 |
| Han Chinese in Bejing, China (CHB) | 106 | 0.262 | 0.999 |  | 0.004 | 0.003 |
| Japanese in Tokyo, Japan (JPT) | 105 | 0.312 | 0.469 |  | 0.000 | 0.001 |
| Kinh in Ho Chi Minh City, Vietnam (KHV) | 101 | 0.338 | 0.260 |  | 0.000 | 0.001 |
| Southern Han Chinese, China (CHS) | 112 | 0.376 | 0.093 |  | 0.000 | 0.001 |
| South Asian |  |  |  |  |  |  |
| Bengali in Bangladesh (BEB) | 86 | 0.227 | 0.660 |  | 0.000 | 0.004 |
| Gujarati Indian in Houston,TX (GIH) | 106 | 0.238 | 0.760 |  | 0.009 | 0.006 |
| Indian Telugu in the UK (ITU) | 103 | 0.289 | 0.661 |  | 0.019 | 0.020 |
| Punjabi in Lahore,Pakistan (PJL) | 96 | 0.281 | 0.772 |  | 0.031 | 0.066 |
| Sri Lankan Tamil in the UK (STU) | 103 | 0.206 | 0.438 |  | 0.009 | 0.006 |
| African |  |  |  |  |  |  |
| African Ancestry in Southwest US (ASW) | 66 | 0.221 | 0.582 |  | 0.032 | 0.115 |
| African Caribbean in Barbados (ACB) | 96 | 0.177 | 0.210 |  | 0.005 | 0.004 |
| Esan in Nigeria (ESN) | 99 | 0.212 | 0.442 |  | 0.000 | 0.002 |
| Gambian in Western Division, The Gambia (GWD) | 113 | 0.199 | 0.339 |  | 0.000 | 0.001 |
| Luhya in Webuye, Kenya (LWK) | 116 | 0.131 | 0.026 |  | 0.000 | 0.001 |
| Mende in Sierra Leone (MSL) | 85 | 0.159 | 0.125 |  | 0.000 | 0.002 |
| Yoruba in Ibadan, Nigeria (YRI) | 116 | 0.162 | 0.096 |  | 0.000 | 0.001 |
| Americas |  |  |  |  |  |  |
| Colombian in Medellin, Colombia (CLM) | 95 | 0.213 | 0.447 |  | 0.074 | 0.550 |
| Mexican Ancestry in Los Angeles, California (MXL) | 69 | 0.203 | 0.398 |  | 0.070 | 0.523 |
| Peruvian in Lima, Peru (PEL) | 86 | 0.306 | 0.489 |  | 0.035 | 0.101 |
| Puerto Rican in Puerto Rico (PUR) | 105 | 0.226 | 0.646 |  | 0.129 | 0.554 |

**Supplementary Table S2:** Combined allelic load matrix.

|  |  |  |
| --- | --- | --- |
| ***Allelic Load Score*** | **rs12155594** | **rs4281084** |
| 0 | CC | GG |
| 1 | C**T** | GG |
|  | CC | G**A** |
| 2 | C**T** | G**A** |
|  | **TT** | GG |
|  | CC | **AA** |
| 3 | **TT** | G**A** |
|  | C**T** | **AA** |
| 4 | **TT** | **AA** |

Bolded alleles are designated 'risk conferring', aligned with our previous

results ([Bousman et al., 2013](#_ENREF_3))

**Supplementary Table S3.** Demographic and clinical

characteristics of cases by age of illness onset

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Age of illness onset** | |  |  |
| **Characteristic** | **≤ 25 (n=177)** | **> 25 (n=80)** |  | **p** |
| Age, mean (sd) years | 35 (10) | 45 (9) |  | <0.001 |
| Sex, % (n) female | 27 (47) | 38 (30) |  | 0.076 |
| Education, mean (sd) years | 13 (3) | 14 (3) |  | 0.001 |
| WASI IQ, mean (sd) years | 104 (15) | 108 (14) |  | 0.021 |
| Current antipsychotic use, % (n) | 85 (151) | 88 (70) |  | 0.640 |
| Current tobacco use, % (n) | 60 (106) | 66 (53) |  | 0.884 |
| Alcohol use in past year, % (n) | 83 (147) | 85 (68) |  | 0.918 |
| Cannabis use in past year, % (n) | 41 (73) | 35 (28) |  | 0.355 |
| Amphetamine use in past year, % (n) | 82 (145) | 85 (68) |  | 0.693 |

**Supplementary Table S3:** P-values for volumetric analyses by region and genotype

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **rs4281084** | |  | **rs12155594** | |  | **Combined Allelic Load** | |
|  | **Raw (B-H) P-value** | |  | **Raw (B-H) P-value** | |  | **Raw (B-H) P-value** | |
| **Region** | **Main Effect** | **Interaction w/ Case-Control Status** |  | **Main Effect** | **Interaction w/ Case-Control Status** |  | **Main Effect** | **Interaction w/ Case-Control Status** |
| CortexVol | 0.864 | 0.822 |  | 0.583 | 0.578 |  | 0.747 | 0.739 |
| SubCortGrayVol | 0.385 | 0.769 |  | 0.867 | 0.297 |  | 0.120 | 0.104 |
| SupraTentorialVol | 0.888 | 0.608 |  | 0.487 | 0.825 |  | 0.605 | 0.855 |
| TotalGrayVol | 0.603 | 0.735 |  | 0.837 | 0.985 |  | 0.370 | 0.923 |
| Left-Accumbens | 0.220 | **0.014** (1.00) |  | 0.394 | 0.108 |  | 0.341 | **0.004** (0.37) |
| Left-Amygdala | 0.358 | 0.261 |  | 0.645 | 0.081 |  | 0.984 | 0.978 |
| Left-bankssts | 0.988 | 0.927 |  | 0.973 | 0.730 |  | 0.927 | 0.623 |
| Left-caudalanteriorcingulate | 0.523 | 0.780 |  | 0.119 | 0.072 |  | 0.333 | 0.801 |
| Left-caudalmiddlefrontal | 0.480 | 0.718 |  | 0.800 | 0.970 |  | 0.702 | 0.801 |
| Left-Caudate | 0.608 | 0.738 |  | 0.316 | 1.000 |  | 0.830 | 0.663 |
| Left-Cerebellum-Cortex | 0.155 | 0.801 |  | 0.911 | 0.350 |  | 0.174 | 0.152 |
| Left-choroid-plexus | 0.718 | 0.661 |  | 0.859 | 0.636 |  | 0.889 | 0.382 |
| Left-CortexVol | 0.795 | 0.925 |  | 0.592 | 0.631 |  | 0.566 | 0.773 |
| Left-cuneus | 0.725 | 0.073 |  | 0.052 | **0.044** (1.00) |  | 0.777 | 0.897 |
| Left-entorhinal | 0.378 | 0.779 |  | 0.312 | 0.505 |  | 0.071 | 0.278 |
| Left-frontalpole | 0.699 | 0.401 |  | 0.176 | 0.295 |  | 0.438 | 0.685 |
| Left-fusiform | 0.821 | 0.102 |  | 0.889 | 0.682 |  | 0.463 | 0.222 |
| Left-Hippocampus | 0.924 | 0.322 |  | 0.719 | 0.944 |  | 0.979 | 0.775 |
| Left-Inf-Lat-Vent | 0.561 | 0.574 |  | 0.456 | 0.166 |  | 0.537 | 0.183 |
| Left-inferiorparietal | 0.772 | 0.939 |  | 0.857 | 0.563 |  | 0.203 | 0.809 |
| Left-inferiortemporal | 0.200 | 0.103 |  | 0.629 | 0.611 |  | 0.550 | 0.802 |
| Left-insula | 0.744 | 0.250 |  | 0.931 | 0.618 |  | 0.711 | 0.256 |
| Left-isthmuscingulate | 0.531 | 0.652 |  | 0.541 | 0.580 |  | 0.679 | 0.931 |
| Left-lateraloccipital | 0.584 | 0.122 |  | 0.154 | **0.016** (1.00) |  | 0.796 | 0.325 |
| Left-lateralorbitofrontal | 0.759 | 0.626 |  | 0.415 | 0.638 |  | 0.728 | 0.967 |
| Left-lingual | 0.629 | 0.754 |  | 0.698 | 0.508 |  | 0.773 | 0.931 |
| Left-medialorbitofrontal | 0.117 | **0.022** (1.00) |  | 0.996 | 0.878 |  | 0.193 | 0.342 |
| Left-middletemporal | 0.514 | 0.771 |  | 0.977 | 0.934 |  | 0.454 | 0.455 |
| Left-Pallidum | 0.197 | 0.406 |  | 0.190 | 0.923 |  | 0.434 | 0.747 |
| Left-paracentral | 0.584 | 0.279 |  | 0.690 | 0.070 |  | 0.396 | 0.058 |
| Left-parahippocampal | 0.896 | 0.778 |  | 0.957 | 0.868 |  | 0.719 | 0.263 |
| Left-parsopercularis | 0.920 | 0.903 |  | 0.904 | 0.413 |  | 0.975 | 0.719 |
| Left-parsorbitalis | 0.322 | 0.732 |  | 0.154 | 0.127 |  | 0.880 | 0.931 |
| Left-parstriangularis | 0.641 | 0.753 |  | 0.715 | 0.613 |  | 0.302 | 0.547 |
| Left-pericalcarine | 0.925 | 0.458 |  | 0.445 | 0.080 |  | 0.453 | 0.608 |
| Left-postcentral | 0.677 | 0.809 |  | 0.787 | 0.813 |  | 0.935 | 0.558 |
| Left-posteriorcingulate | 0.399 | 0.564 |  | 0.060 | 0.144 |  | 0.944 | 0.875 |
| Left-precentral | 0.830 | 0.527 |  | 0.168 | 0.244 |  | 0.869 | 0.124 |
| Left-precuneus | 0.247 | 0.835 |  | 0.673 | 0.195 |  | 0.465 | 0.640 |
| Left-Putamen | 0.822 | 0.466 |  | 0.489 | 0.747 |  | 0.638 | 0.673 |
| Left-rostralanteriorcingulate | 0.543 | 0.059 |  | 0.392 | 0.833 |  | 0.549 | 0.174 |
| Left-rostralmiddlefrontal | 0.151 | 0.499 |  | 0.099 | 0.551 |  | 0.284 | 0.226 |
| Left-superiorfrontal | 0.304 | 0.210 |  | 0.403 | 0.398 |  | 0.844 | 0.689 |
| Left-superiorparietal | 0.249 | 0.422 |  | 0.572 | 0.385 |  | 0.618 | 0.875 |
| Left-superiortemporal | 0.365 | 0.480 |  | 0.822 | 0.391 |  | 0.783 | 0.634 |
| Left-supramarginal | 0.094 | 0.716 |  | 0.596 | 0.665 |  | 0.246 | 0.566 |
| Left-temporalpole | 0.472 | 0.533 |  | 0.917 | 0.907 |  | 0.066 | 0.092 |
| Left-Thalamus-Proper | 0.545 | 0.925 |  | 0.482 | 0.478 |  | 0.378 | 0.868 |
| Left-transversetemporal | 0.723 | 0.534 |  | 0.779 | 0.780 |  | 0.736 | 0.611 |
| Left-VentralDC | 0.946 | 0.344 |  | 0.064 | 0.172 |  | 0.759 | 0.205 |
| Right-Accumbens | 0.155 | 0.249 |  | **0.045** (1.00) | 0.137 |  | 0.063 | 0.134 |
| Right-Amygdala | 0.721 | 0.118 |  | 0.538 | 0.828 |  | 0.936 | 0.357 |
| Right-bankssts | 0.551 | 0.580 |  | 0.830 | 0.343 |  | 0.447 | 0.430 |
| Right-caudalanteriorcingulate | 0.898 | 0.378 |  | 0.697 | 0.845 |  | 0.467 | 0.756 |
| Right-caudalmiddlefrontal | 0.749 | 0.561 |  | 0.399 | 0.586 |  | 0.425 | 0.334 |
| Right-Caudate | 0.297 | 0.609 |  | 0.226 | 0.974 |  | 0.243 | 0.826 |
| Right-Cerebellum-Cortex | 0.259 | 0.897 |  | 0.675 | 0.129 |  | **0.029** (1.00) | 0.084 |
| Right-choroid-plexus | 0.959 | 0.660 |  | 0.775 | 0.989 |  | 0.646 | 0.587 |
| Right-CortexVol | 0.850 | 0.700 |  | 0.574 | 0.530 |  | 0.892 | 0.696 |
| Right-cuneus | 0.486 | 0.121 |  | 0.452 | 0.060 |  | 0.802 | 0.468 |
| Right-entorhinal | 0.547 | 0.256 |  | 0.397 | 0.536 |  | 0.270 | 0.174 |
| Right-frontalpole | 0.411 | 0.460 |  | 0.983 | 0.967 |  | 0.235 | 0.289 |
| Right-fusiform | 0.278 | 0.186 |  | 0.537 | 0.477 |  | 0.583 | 0.470 |
| Right-Hippocampus | 0.336 | 0.142 |  | 0.097 | 0.258 |  | 0.425 | 0.253 |
| Right-Inf-Lat-Vent | 0.314 | 0.276 |  | 0.067 | 0.301 |  | 0.164 | 0.986 |
| Right-inferiorparietal | 0.883 | 0.668 |  | 0.790 | 0.823 |  | 0.910 | 0.460 |
| Right-inferiortemporal | **0.023** (1.00) | 0.132 |  | 0.787 | 0.975 |  | **0.025** (1.00) | 0.213 |
| Right-insula | 0.163 | 0.281 |  | 0.768 | 0.944 |  | 0.357 | 0.492 |
| Right-isthmuscingulate | 0.183 | 0.086 |  | 0.640 | 0.619 |  | 0.851 | 0.545 |
| Right-lateraloccipital | 0.072 | 0.433 |  | 0.381 | 0.098 |  | 0.441 | 0.561 |
| Right-lateralorbitofrontal | 0.555 | 0.996 |  | 0.304 | 0.613 |  | 0.150 | 0.181 |
| Right-lingual | 0.698 | 0.566 |  | 0.217 | **0.031** (1.00) |  | 0.556 | 0.688 |
| Right-medialorbitofrontal | 0.266 | 0.119 |  | 0.684 | 0.822 |  | 0.790 | 0.511 |
| Right-middletemporal | 0.864 | 0.648 |  | 0.909 | 0.914 |  | 0.389 | 0.865 |
| Right-Pallidum | 0.725 | 0.903 |  | 0.564 | 0.795 |  | 0.474 | 0.824 |
| Right-paracentral | 0.901 | 0.572 |  | 0.542 | 0.649 |  | 0.581 | 0.263 |
| Right-parahippocampal | 0.820 | 0.435 |  | 0.839 | 0.536 |  | 0.666 | 0.308 |
| Right-parsopercularis | 0.823 | 0.559 |  | 0.421 | 0.312 |  | 0.916 | 0.903 |
| Right-parsorbitalis | 0.816 | 0.116 |  | 0.341 | 0.795 |  | 0.342 | 0.065 |
| Right-parstriangularis | 0.970 | 0.382 |  | 0.314 | 0.302 |  | 0.956 | 0.973 |
| Right-pericalcarine | 0.829 | 0.132 |  | 0.462 | 0.136 |  | 0.606 | 0.738 |
| Right-postcentral | 0.825 | 0.876 |  | 0.514 | 0.395 |  | 0.873 | 0.676 |
| Right-posteriorcingulate | 0.966 | 0.969 |  | 0.473 | 0.693 |  | 0.792 | 0.851 |
| Right-precentral | 0.965 | 0.611 |  | 0.846 | 0.680 |  | 0.742 | 0.456 |
| Right-precuneus | 0.554 | 0.758 |  | 0.774 | 0.502 |  | 0.464 | 0.897 |
| Right-Putamen | 0.406 | 0.188 |  | 0.338 | 0.564 |  | 0.207 | 0.173 |
| Right-rostralanteriorcingulate | 0.898 | 0.802 |  | 0.648 | 0.246 |  | 0.330 | 0.535 |
| Right-rostralmiddlefrontal | 0.365 | 0.842 |  | 0.058 | 0.627 |  | 0.235 | 0.343 |
| Right-superiorfrontal | 0.710 | 0.517 |  | 0.804 | 0.724 |  | 0.901 | 0.344 |
| Right-superiorparietal | **0.003** (0.28) | **0.043** (0.99) |  | 0.350 | 0.210 |  | 0.105 | 0.500 |
| Right-superiortemporal | 0.274 | 0.178 |  | 0.126 | 0.195 |  | 0.180 | 0.063 |
| Right-supramarginal | 0.596 | 0.707 |  | 0.868 | 0.739 |  | 0.243 | 0.821 |
| Right-temporalpole | 0.222 | 0.240 |  | 0.893 | 0.839 |  | 0.550 | 0.242 |
| Right-Thalamus-Proper | 0.945 | 0.647 |  | 0.855 | 0.869 |  | 0.868 | 0.931 |
| Right-transversetemporal | **0.036** (1.00) | **0.035** (1.00) |  | 0.716 | 0.714 |  | 0.612 | 0.475 |
| Right-VentralDC | 0.464 | 0.795 |  | 0.850 | 0.227 |  | 0.717 | 0.420 |

B-H, Benjamini-Hochberg corrected p-value

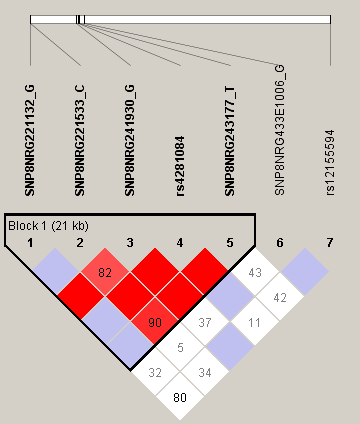
**Supplementary Table S4:** P-values for thickness analyses by region and genotype

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **rs4281084** | |  | **rs12155594** | |  | **Combined Allelic Load** | |
|  | **Raw (B-H) P-value** | |  | **Raw (B-H) P-value** | |  | **Raw (B-H) P-value** | |
| **Region** | **Main Effect** | **Interaction w/ Case-Control Status** |  | **Main Effect** | **Interaction w/ Case-Control Status** |  | **Main Effect** | **Interaction w/ Case-Control Status** |
| Left-bankssts | 0.798 | 0.681 |  | 0.386 | 0.501 |  | 0.823 | 0.851 |
| Left-caudalanteriorcingulate | 0.162 | 0.954 |  | 0.539 | 0.307 |  | 0.192 | 0.807 |
| Left-caudalmiddlefrontal | 0.442 | 0.357 |  | 0.378 | 0.249 |  | 0.635 | 0.844 |
| Left-cuneus | 0.802 | 0.483 |  | 0.114 | 0.148 |  | 0.868 | 0.630 |
| Left-entorhinal | 0.492 | 0.062 |  | 0.892 | 0.395 |  | 0.191 | **0.004** (0.14) |
| Left-frontalpole | 0.854 | 0.681 |  | 0.368 | 0.527 |  | 0.464 | 0.988 |
| Left-fusiform | 0.947 | 0.511 |  | 0.653 | 0.707 |  | 0.893 | 0.540 |
| Left-inferiorparietal | 0.099 | 0.298 |  | 0.518 | 0.670 |  | 0.410 | 0.912 |
| Left-inferiortemporal | 0.555 | 0.121 |  | 0.416 | 0.197 |  | 0.428 | 0.703 |
| Left-insula | 0.948 | 0.540 |  | 0.829 | 0.955 |  | 0.911 | 0.534 |
| Left-isthmuscingulate | **0.045** (1.00) | **0.007** (0.48) |  | **0.017** (1.00) | **0.007** (0.48) |  | **0.027** (1.00) | **0.001** (0.07) |
| Left-lateraloccipital | 0.823 | 0.919 |  | 0.171 | 0.481 |  | 0.929 | 0.951 |
| Left-lateralorbitofrontal | 0.731 | 0.648 |  | 0.900 | 0.809 |  | 0.588 | 0.474 |
| Left-lingual | 0.760 | 0.771 |  | 0.143 | 0.649 |  | 0.908 | 0.554 |
| Left-medialorbitofrontal | 0.501 | 0.413 |  | 0.783 | 0.330 |  | 0.671 | 0.741 |
| Left-middletemporal | 0.530 | 0.561 |  | 0.608 | 0.358 |  | 0.831 | 0.989 |
| Left-paracentral | 0.098 | 0.194 |  | 0.503 | 0.880 |  | 0.333 | 0.414 |
| Left-parahippocampal | 0.822 | 0.482 |  | 0.669 | 0.774 |  | 0.581 | 0.623 |
| Left-parsopercularis | 0.636 | 0.944 |  | 0.107 | 0.223 |  | 0.921 | 0.645 |
| Left-parsorbitalis | 0.681 | 0.630 |  | 0.216 | 0.564 |  | 0.134 | 0.649 |
| Left-parstriangularis | 0.904 | 0.435 |  | 0.305 | 0.181 |  | 0.672 | 0.390 |
| Left-pericalcarine | 0.633 | 0.469 |  | 0.396 | 0.398 |  | 0.701 | 0.523 |
| Left-postcentral | 0.177 | 0.358 |  | 0.644 | 0.886 |  | 0.493 | 0.828 |
| Left-posteriorcingulate | 0.505 | 0.111 |  | 0.779 | 0.802 |  | 0.897 | 0.103 |
| Left-precentral | 0.492 | 0.558 |  | 0.142 | 0.266 |  | 0.775 | 0.785 |
| Left-precuneus | 0.070 | 0.640 |  | 0.774 | 0.882 |  | 0.691 | 0.656 |
| Left-rostralanteriorcingulate | 0.137 | 0.853 |  | 0.392 | 0.878 |  | 0.066 | 0.272 |
| Left-rostralmiddlefrontal | 0.941 | 0.967 |  | 0.307 | 0.309 |  | 0.408 | 0.349 |
| Left-superiorfrontal | 0.449 | 0.443 |  | 0.288 | 0.278 |  | 0.958 | 0.878 |
| Left-superiorparietal | **0.028** (0.95) | 0.256 |  | 0.067 | 0.181 |  | 0.093 | 0.251 |
| Left-superiortemporal | 0.331 | 0.668 |  | 0.949 | 0.691 |  | 0.715 | 0.664 |
| Left-supramarginal | 0.153 | 0.745 |  | 0.520 | 0.613 |  | 0.108 | 0.197 |
| Left-temporalpole | 0.821 | 0.847 |  | 0.747 | 0.974 |  | 0.801 | 0.740 |
| Left-transversetemporal | 0.205 | 0.080 |  | 0.549 | 0.556 |  | 0.571 | 0.344 |
| Right-bankssts | 0.608 | 0.704 |  | 0.345 | 0.990 |  | 0.863 | 0.765 |
| Right-caudalanteriorcingulate | 0.583 | 1.000 |  | 0.894 | 0.963 |  | 0.519 | 0.492 |
| Right-caudalmiddlefrontal | 0.801 | 0.728 |  | **0.044** (0.75) | **0.025** (0.43) |  | 0.881 | 0.932 |
| Right-cuneus | 0.423 | **0.04** (0.91) |  | 0.388 | 0.738 |  | 0.777 | 0.143 |
| Right-entorhinal | 0.978 | 0.741 |  | 0.462 | 0.448 |  | 0.768 | 0.546 |
| Right-frontalpole | 0.489 | 0.427 |  | 0.712 | 0.986 |  | 0.161 | 0.190 |
| Right-fusiform | 0.482 | 0.997 |  | 0.292 | 0.304 |  | 0.116 | 0.225 |
| Right-inferiorparietal | 0.130 | 0.714 |  | 0.508 | 0.723 |  | 0.776 | 0.685 |
| Right-inferiortemporal | 0.924 | 0.732 |  | 0.575 | 0.664 |  | 0.945 | 0.830 |
| Right-insula | 0.359 | 0.766 |  | 0.889 | 0.609 |  | 0.988 | 0.773 |
| Right-isthmuscingulate | 0.179 | 0.812 |  | **0.017** (0.58) | **0.007** (0.24) |  | 0.752 | 0.819 |
| Right-lateraloccipital | 0.558 | 0.877 |  | 0.074 | 0.364 |  | 0.605 | 0.650 |
| Right-lateralorbitofrontal | 0.994 | 0.943 |  | 0.488 | 0.527 |  | 0.350 | 0.267 |
| Right-lingual | 0.396 | 0.378 |  | 0.523 | 0.844 |  | 0.761 | 0.880 |
| Right-medialorbitofrontal | 0.457 | 0.987 |  | 0.569 | 0.914 |  | 0.354 | 0.958 |
| Right-middletemporal | 0.824 | 0.764 |  | 0.650 | 0.961 |  | 0.592 | 0.969 |
| Right-paracentral | 0.539 | 0.205 |  | 0.195 | 0.416 |  | 0.512 | 0.266 |
| Right-parahippocampal | 0.784 | 0.392 |  | 0.843 | 0.985 |  | 0.948 | 0.484 |
| Right-parsopercularis | 0.153 | 0.105 |  | 0.580 | 0.679 |  | 0.380 | 0.338 |
| Right-parsorbitalis | 0.510 | 0.372 |  | 0.964 | 0.644 |  | 0.092 | **0.032** (0.73) |
| Right-parstriangularis | 0.723 | 0.489 |  | 0.475 | 0.367 |  | 0.978 | 0.890 |
| Right-pericalcarine | 0.126 | **0.016** (0.54) |  | 0.793 | 0.843 |  | 0.515 | 0.655 |
| Right-postcentral | 0.438 | 0.363 |  | 0.324 | 0.445 |  | 0.383 | 0.881 |
| Right-posteriorcingulate | 0.252 | 0.083 |  | 0.909 | 0.993 |  | 0.351 | 0.521 |
| Right-precentral | 0.346 | 0.354 |  | 0.149 | 0.296 |  | 0.657 | 0.781 |
| Right-precuneus | 0.093 | 0.233 |  | 0.986 | 0.987 |  | 0.576 | 0.429 |
| Right-rostralanteriorcingulate | 0.338 | 0.267 |  | **0.036** (0.82) | 0.312 |  | 0.186 | 0.350 |
| Right-rostralmiddlefrontal | 0.662 | 0.730 |  | 0.549 | 0.648 |  | 0.803 | 0.775 |
| Right-superiorfrontal | 0.381 | 0.551 |  | 0.230 | 0.474 |  | 0.951 | 0.628 |
| Right-superiorparietal | **0.006** (0.41) | **0.041** (0.69) |  | 0.224 | 0.495 |  | **0.041** (1.00) | 0.096 |
| Right-superiortemporal | 0.425 | 0.467 |  | 0.793 | 0.623 |  | 0.557 | 0.384 |
| Right-supramarginal | 0.071 | 0.116 |  | 0.611 | 0.655 |  | 0.250 | 0.194 |
| Right-temporalpole | 0.749 | 0.591 |  | 0.842 | 0.790 |  | 0.791 | 0.751 |
| Right-transversetemporal | 0.148 | 0.091 |  | 0.080 | **0.02** (0.45) |  | 0.462 | 0.993 |

B-H, Benjamini-Hochberg corrected p-value

**Supplementary Table S5:** P-values for surface area analyses by region and genotype

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **rs4281084** | |  | **rs12155594** | |  | **Combined Allelic Load** | |
|  | **Raw (B-H) P-value** | |  | **Raw (B-H) P-value** | |  | **Raw (B-H) P-value** | |
| **Region** | **Main Effect** | **Interaction w/ Case-Control Status** |  | **Main Effect** | **Interaction w/ Case-Control Status** |  | **Main Effect** | **Interaction w/ Case-Control Status** |
| Left-bankssts | 0.884 | 0.883 |  | 0.932 | 0.524 |  | 0.926 | 0.828 |
| Left-caudalanteriorcingulate | 0.675 | 0.775 |  | 0.148 | 0.149 |  | 0.600 | 0.891 |
| Left-caudalmiddlefrontal | 0.290 | 0.929 |  | 0.990 | 0.835 |  | 0.744 | 0.792 |
| Left-cuneus | 0.995 | 0.280 |  | 0.444 | 0.294 |  | 0.677 | 0.957 |
| Left-entorhinal | 0.743 | 0.629 |  | 0.208 | 0.313 |  | 0.335 | 0.731 |
| Left-frontalpole | 0.421 | 0.381 |  | 0.530 | 0.669 |  | 0.258 | 0.362 |
| Left-fusiform | 0.466 | 0.116 |  | 0.334 | 0.317 |  | 0.389 | 0.515 |
| Left-inferiorparietal | 0.239 | 0.679 |  | 0.556 | 0.431 |  | 0.238 | 0.776 |
| Left-inferiortemporal | 0.209 | 0.197 |  | 0.752 | 0.701 |  | 0.400 | 0.887 |
| Left-insula | 0.575 | 0.071 |  | 0.890 | 0.831 |  | 0.787 | 0.118 |
| Left-isthmuscingulate | 0.321 | 0.243 |  | 0.948 | 0.776 |  | 0.707 | 0.378 |
| Left-lateraloccipital | 0.348 | 0.063 |  | 0.586 | **0.035** (0.60) |  | 0.589 | 0.183 |
| Left-lateralorbitofrontal | 0.349 | 0.439 |  | 0.479 | 0.919 |  | 0.650 | 0.972 |
| Left-lingual | 0.782 | 0.835 |  | 0.930 | 0.639 |  | 0.588 | 0.627 |
| Left-medialorbitofrontal | 0.155 | 0.094 |  | 0.953 | 0.900 |  | 0.160 | 0.496 |
| Left-middletemporal | 0.399 | 0.626 |  | 0.962 | 0.522 |  | 0.588 | 0.501 |
| Left-paracentral | 0.955 | 0.750 |  | 0.350 | **0.024** (0.82) |  | 0.653 | 0.075 |
| Left-parahippocampal | 0.335 | 0.844 |  | 0.677 | 0.679 |  | 0.799 | 0.556 |
| Left-parsopercularis | 0.966 | 0.964 |  | 0.856 | 0.813 |  | 0.985 | 0.750 |
| Left-parsorbitalis | 0.278 | 0.890 |  | 0.718 | 0.210 |  | 0.936 | 0.668 |
| Left-parstriangularis | 0.549 | 0.503 |  | 0.980 | 0.932 |  | 0.426 | 0.796 |
| Left-pericalcarine | 0.894 | 0.612 |  | 0.597 | 0.100 |  | 0.472 | 0.734 |
| Left-postcentral | 0.751 | 0.680 |  | 0.729 | 0.373 |  | 0.854 | 0.259 |
| Left-posteriorcingulate | 0.360 | 0.698 |  | 0.103 | 0.134 |  | 0.987 | 0.602 |
| Left-precentral | 0.615 | 0.210 |  | 0.809 | 0.380 |  | 0.450 | **0.012** (0.82) |
| Left-precuneus | 0.914 | 0.501 |  | 0.339 | **0.039** (0.44) |  | 0.374 | 0.264 |
| Left-rostralanteriorcingulate | 0.240 | 0.094 |  | 0.434 | 0.723 |  | **0.048** (1.00) | **0.046** (1.00) |
| Left-rostralmiddlefrontal | **0.043** (0.97) | 0.428 |  | 0.493 | 0.945 |  | 0.227 | 0.607 |
| Left-superiorfrontal | 0.509 | 0.402 |  | 0.253 | 0.118 |  | 0.845 | 0.719 |
| Left-superiorparietal | 0.966 | 0.748 |  | **0.028** (1.00) | **0.036** (0.49) |  | 0.714 | 0.805 |
| Left-superiortemporal | 0.725 | 0.623 |  | 0.868 | 0.179 |  | 0.971 | 0.512 |
| Left-supramarginal | **0.013** (0.44) | 0.580 |  | 0.876 | 0.527 |  | **0.027** (0.92) | 0.640 |
| Left-temporalpole | 0.785 | 0.321 |  | 0.700 | 0.774 |  | 0.050 | **0.034** (1.00) |
| Left-transversetemporal | 0.726 | 0.741 |  | 0.885 | 0.767 |  | 0.644 | 0.896 |
| Right-bankssts | 0.298 | 0.192 |  | 0.905 | 0.204 |  | 0.340 | 0.252 |
| Right-caudalanteriorcingulate | 0.739 | 0.290 |  | 0.800 | 0.685 |  | 0.344 | 0.478 |
| Right-caudalmiddlefrontal | 0.382 | 0.314 |  | 0.918 | 0.973 |  | 0.210 | 0.290 |
| Right-cuneus | 0.827 | 0.857 |  | 0.512 | **0.024** (0.54) |  | 0.363 | 0.321 |
| Right-entorhinal | 0.730 | 0.393 |  | 0.950 | 0.969 |  | 0.620 | 0.917 |
| Right-frontalpole | 0.603 | 0.128 |  | 0.879 | 0.991 |  | 0.549 | 0.477 |
| Right-fusiform | 0.702 | 0.265 |  | 0.533 | 0.819 |  | 0.593 | 0.610 |
| Right-inferiorparietal | 0.267 | 0.514 |  | 0.626 | 0.498 |  | 0.705 | 0.561 |
| Right-inferiortemporal | **0.011** (0.75) | 0.153 |  | 0.859 | 0.948 |  | **0.011** (0.75) | 0.158 |
| Right-insula | 0.376 | 0.439 |  | 0.275 | 0.754 |  | 0.706 | 0.482 |
| Right-isthmuscingulate | 0.737 | 0.123 |  | 0.241 | 0.317 |  | 0.839 | 0.291 |
| Right-lateraloccipital | 0.092 | 0.234 |  | 0.500 | 0.087 |  | 0.703 | 0.807 |
| Right-lateralorbitofrontal | 0.390 | 0.852 |  | 0.717 | 0.527 |  | 0.749 | 0.843 |
| Right-lingual | 0.916 | 0.862 |  | 0.302 | **0.014** (0.95) |  | 0.091 | 0.378 |
| Right-medialorbitofrontal | 0.364 | 0.052 |  | 0.957 | 0.934 |  | 0.566 | 0.115 |
| Right-middletemporal | 0.337 | 0.622 |  | 0.956 | 0.892 |  | 0.200 | 0.704 |
| Right-paracentral | 0.548 | 0.682 |  | 0.634 | 0.628 |  | 0.636 | 0.168 |
| Right-parahippocampal | 0.938 | 0.905 |  | 0.792 | 0.747 |  | 0.659 | 0.728 |
| Right-parsopercularis | 0.992 | 0.807 |  | 0.431 | 0.405 |  | 0.978 | 0.995 |
| Right-parsorbitalis | 0.355 | 0.074 |  | 0.731 | 0.578 |  | 0.870 | 0.355 |
| Right-parstriangularis | 0.663 | 0.456 |  | 0.423 | 0.456 |  | 0.954 | 0.997 |
| Right-pericalcarine | 0.864 | 0.793 |  | 0.609 | 0.107 |  | 0.339 | 0.856 |
| Right-postcentral | 0.361 | 0.509 |  | 0.715 | 0.226 |  | 0.482 | 0.449 |
| Right-posteriorcingulate | 0.808 | 0.831 |  | 0.401 | 0.728 |  | 0.852 | 0.908 |
| Right-precentral | 0.699 | 0.956 |  | 0.168 | 0.119 |  | 0.655 | 0.301 |
| Right-precuneus | 0.697 | 0.725 |  | 0.830 | 0.531 |  | 0.269 | 0.305 |
| Right-rostralanteriorcingulate | 0.911 | 0.714 |  | 0.368 | 0.329 |  | 0.191 | 0.324 |
| Right-rostralmiddlefrontal | 0.153 | 0.644 |  | 0.229 | 0.806 |  | 0.069 | 0.348 |
| Right-superiorfrontal | 0.469 | 0.955 |  | 0.405 | 0.169 |  | 0.890 | 0.320 |
| Right-superiorparietal | 0.186 | 0.359 |  | 0.067 | **0.045** (0.44) |  | 0.637 | 0.600 |
| Right-superiortemporal | 0.797 | 0.305 |  | 0.054 | 0.381 |  | 0.603 | 0.318 |
| Right-supramarginal | 0.584 | 0.569 |  | 0.915 | 0.875 |  | 0.340 | 0.938 |
| Right-temporalpole | 0.740 | 0.385 |  | 0.710 | 0.512 |  | 0.707 | 0.271 |
| Right-transversetemporal | 0.135 | 0.108 |  | 0.772 | 0.302 |  | 0.599 | 0.428 |

B-H, Benjamini-Hochberg corrected p-value ****

**Supplementary Figure S1**. Linkage disequilibrium (D’) between the five HapICE SNPs and the two SNPs associated with psychosis onset (rs4281084 and rs12155594). The most frequent haplotype (GCGGT, 33%) contained all the risk alleles from the four HapICE SNPs, plus the major allele (G) for rs4281084. Linkage disequilibrium estimates for rs12155594 are based on the major C allele. The block represented was determined via the solid spline LD method in HAPLOVIEW ([Barrett et al., 2005](#_ENREF_2)).

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