**Supplementary materials**

**Methods**

*Genotyping*

For SREBF-1, we studied rs11868035, a C>T (reverse strand) or G>A (forward strand) SNP located in the intervening sequence next to the splicing site between exon 18c and 19c (IVS18c-3C>T). The rs11868035 G/G genotype was associated with schizophrenia [[1](#_ENREF_1)]. For SREBF-2, we studied rs1052717, a G>A SNP at nucleotide +414 of intron 11 (IVS11+414 G>A) which has been associated with schizophrenia [[1](#_ENREF_1)].

DNA was manually extracted from whole blood, using the “Illustra blood genomic Prep Midi Flow kit” (GE Healthcare, Milan, Italy). To identify the single nucleotide polymorphism G/A rs11868035, a standard Polymerase Chain Reaction (PCR) was performed with the following primers: 5'- GAGGAGGCTTCTTTGCTGTG -3' and 5'- GGGTCAGTTGTCCCTTCTCA -3'. Instead for the identification of the single nucleotide polymorphism A/G rs1052717, a standard Polymerase Chain Reaction (PCR) was performed with the following primers: 5'- CATTTTGGTCCCCTGAGGTA -3' and 5'- TCGTCTGACCTGAGCTCCTT-3'. The PCR was carried out in a 10 μl volume containing 150 ng genomic DNA, 1 μl of 1× Hot Master Taq Buffer with Mg++ (Eppendorf), 0.1 μl of each primer [50 uM], 1 μl of dNTPs [200 μM], 0.1 μl of Hot Master Taq [5U/ μl] (Eppendorf) and 0.5 μl of Dimethyl sulfoxide (DMSO). After an initial step of 3 min at 94 °C, 35 cycles of amplification (30 s at 94 °C, 30 s at 57 °C, 30 s at 70 °C) and a final extension step of 6 min at 70 °C were performed. The amplified fragment was then purified by Multi-Screen Colum Loader (MILLIPORE), filled up and packaged with Sephadex G-50 (Sigma-Aldrich's) to remove residual PCR reagents. An aliquot of purified PCR product was then used to perform sequencing reaction, using DYEnamic ET Dye Terminator Cycle Sequencing Kit (GE Healthcare, Milan, Italy). In its turn, sequencing reaction product, was purified following the above mentioned protocol, to remove the excess of fluorescent dyes not incorporated in the DNA fragment and then loaded onto a 48 capillaries genetic analyser (MegaBace 500, GE Healthcare, Milan, Italy).

*Diffusion tensor imaging*

DTI was performed on a 3.0 Tesla scanner (Gyroscan Intera, Philips, Netherlands) using SE Eco-planar imaging (EPI) and the following parameters: TR/TE=8753.89/58 msec, FoV (mm) 231.43 (ap), 126.50 (fh), 240.00 (rl); acquisition matrix 2.14 x 2.71 x 2.31; 55 contiguous, 2.3-mm thick axial slices reconstructed with in-plane pixel size 1.88x1.87 mm; SENSE acceleration factor= 2; 1 b0 and 35 non-collinear directions of the diffusion gradients; b value=900 sec/mm2. Fat saturation was performed to avoid chemical shift artifacts. On the same occasion and using the same magnet 22 Turbo Spin Echo (TSE), T2 axial slices (TR = 3000 ms; TE = 85 ms; flip angle = 90°; turbo factor 15; 5-mm- thick, axial slices with a 512x512 matrix and a 230x230 mm2 field of view) were acquired to rule out brain lesions.

Image analyses and tensor calculations were done using the “Oxford Center for Functional Magnetic Resonance Imaging of the Brain Software Library” (FSL 4.1.4; [www.fmrib.ox.ac.uk/fsl/index.html](http://www.fmrib.ox.ac.uk/fsl/index.html)) [[2](#_ENREF_2),[3](#_ENREF_3)]. Initially, each of the 35 DTI volumes was affine registered to the T2-weighted b=0 volume using FLIRT (FMRIB's Linear Image Registration Tool) [[4](#_ENREF_4)]. This corrected for motion between scans and residual eddy–current distortions present in the diffusion-weighted images. To check head motion, blind researchers manually inspected each volume of every image: scans could be rated 0 if they had little or no detectable motion artifacts, 1 (mild) were rated those with enough motion artifacts to be detectable and resulted in sublte concentric bands, 2 (moderate) had significant banding, whereas rating 3 meant extreme banding and therefore were classified as unreliable for analyses [[5](#_ENREF_5)]. After removing nonbrain tissue [[6](#_ENREF_6)], least-square fits were performed to estimate the FA, eigenvector, and eigenvalue maps. MD was defined as the mean of all three eigenvalues [(λ1 + λ2 + λ3)/3], AD as the principal diffusion eigenvalue (λ1), and RD as the mean of the second and third eigenvalues [(λ2 + λ3)/2]. Next, all individuals' FA volumes were skeletonized and transformed into a common space as used in Tract-Based Spatial Statistics [[7](#_ENREF_7),[8](#_ENREF_8)]. TBSS focuses on the centers of all fiber bundles that are common to the participants (the most compact WM skeleton), therefore increasing the probability that the given spatial voxels contain data from the same part of the same WM tract of each participant. Briefly, all volumes were nonlinearly warped to the FMRIB58\_FA template supplied with FSL (<http://www.fmrib.ox.ac.uk/fsl/tbss/FMRIB58_FA.html>) and normalized to the Montreal Neurological Institute (MNI) space, by using local deformation procedures performed by FMRIB's Non-Linear Image Registration Tool (FNIRT) ([www.fmrib.ox.ac.uk/fsl/fnirt/index.html](http://www.fmrib.ox.ac.uk/fsl/fnirt/index.html)) , a nonlinear registration toolkit which usies a b-spline representation of the registration warp field [[9](#_ENREF_9)]. The common template used in the present study is a high-resolution average of 58 FA volumes from healthy male and female subjects aged 20–50 years. All warped FA volumes were visually inspected for accuracy, which is especially pertinent when analyzing datasets with broad age ranges with relatively large interindividual variability in brain size and architecture. FNIRT has been shown to perform the native-to-standard warping adequately across several age groups, including children and adolescents [[10](#_ENREF_10)]. Next, a mean FA volume of all subjects was generated and thinned to create a mean FA skeleton representing the centers of all common tracts. We thresholded and binarized the mean skeleton at FA >0.20 to reduce the likelihood of partial voluming in the borders between tissue classes, yielding a mask of 137,833 WM voxels. Individual FA values were warped onto this mean skeleton mask by searching perpendicular from the skeleton for maximum FA values. Using maximum FA values from the centers of the tracts further minimizes confounding effects attributable to partial voluming[[7](#_ENREF_7)]. The resulting tract invariant skeletons for each participant were fed into voxelwise permutation-based cross-subject statistics. Similar warping and analyses were used on MD, AD, and RD data sampled from voxels with FA >0,20.

**Legends**

**Figure 1 Supp**. WM areas where SREBF rs11868035 G/G homozygotes showed significantly higher values of FA. Voxels of significant group difference are mapped on the mean FA template.

**Figure 2 Supp.** WM areas where medication load significantly correlated with lower FA and higher water diffusivity. Voxels of significant positive correlation are mapped on the mean FA template.

**Table 1 Supp.** WM areas where SREBF rs11868035 G/G homozygotes showed significantly higher values of FA. Means ± SD values, clusters dimensions (number of voxels, mm3) and involved WM tracts are shown for the WM regions where the two groups significantly differ.

**Table 2 Supp.** WM areas where medication load significantly correlated with lower FA and higher water diffusivity. Mean±SD values, clusters dimensions (number of voxels, mm3) and involved WM tracts are shown for the WM regions where the two groups significantly differ.

**Table 1 Supp**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **DTI**  **measure** | **Numbers of Voxels** | **Signal Peak**  **(x, y, z)** | **White Matter Tracts** | | **Direction of Effect** |
| **Fractional Anisotropy**  **A-Carriers**  0.589±0.184  **GG**  **Homozygotes**  0.514±0.119 | **7982** | **21, 28, 23** | * Anterior corona radiata L * Forceps minor * Genu of corpus callosum R * Body of corpus callosum L * Anterior talamic radiation L * Inferior fronto-occipital fasciculum L * Anterior limb of internal capsule L * Posterior limb of internal capsule L * Retrolenticular part of internal capsule L | * Inferior longitudinal fasciculus, * Posterior thalamic radiation (include optic radiation) L * External capsule, Uncinate fasciculus * Superior longitudinal fasciculus L * Splenium of corpus callosum L * Cingulum L * Cortico-spinal tract L * Splenium of corpus callosum L * Genu of corpus callosum L | GG < A-carriers |
| **1524** | **26, 26, 5** | * Anterior corona radiata R * Genu of corpus callosum R * Inferior fronto-occipital fasciculus R * Anterior limb of internal capsule R * Anterior thalamic radiation R * Posterior limb of internal capsule R * External capsule R * Superior fronto-occipital fasciculus |  |
| **270** | **19, 22, 36** | * Cingulum (cingulate gyrus) R |  |
| **179** | **28, 11, -11** | * External capsule R, * Uncinate fasciculus R, | * Inferior fronto-occipital fasciculus R |
| **176** | **43, -29, -13** | * Sagittal stratum (include inferior fronto-occipital fasciculus) R | * Inferior longitudinal fasciculus R |

**Table 2 Supp**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **DTI**  **measure** | **Number of Voxels** | **Signal Peak**  **(x, y, z)** | **White Matter Tracts** | | | **Direction of Effect** |
| **Fractional**  **Anisotropy**  **A-Carriers**  0.48±0.106  **GG homozygotes**  0.49±0.106 | **18540** | **-15, 4, 33** | * Superior longitudinal fasciculus R * Forceps minor R * Genu of corpus callosum * Body of corpus callosum * Splenium of corpus callosum * Posterior corona radiata R * Anterior corona radiata R * Inferior fronto-occipital fasciculus L * Anterior corona radiata L * Posterior corona radiata L * Cingulum (cingulate gyrus) L | * Superior longitudinal fasciculus L * Corticospinal tract R * Superior corona radiata L, Corticospinal tract L * Inferior longitudinal fasciculus L * Cingulum (cingulate gyrus) R * Forceps minor L * Forceps major * Inferior longitudinal fasciculus L * Inferior fronto-occipital fasciculus R * Anterior thalamic radiation L | | Inverse Correlation |  |
| **Axial Diffusivity**  **A-Carriers**  0.0012  ±  0.000024  **GG homozygotes**  0.0012  ±  0.0000246 | **13018** | **20, 23, -11** | * Uncinate fasciculus R * Anterior corona radiata R * External capsule R * Inferior fronto-occipital fasciculus R * Genu of corpus callosum * Uncinate fasciculus L * Forceps minor * Retrolenticular part of internal capsule R * Superior longitudinal fasciculus R | * Inferior longitudinal fasciculus L * Inferior longitudinal fasciculus R * Body of corpus callosum * Superior corona radiata R * Cingulum (cingulate gyrus) L * Splenium of corpus callosum * Forceps major * Posterior thalamic radiation (include optic radiation) L and R | | Positive correlation |  |
| **2782** | **-17, 22, -12** | * Anterior corona radiata L * Uncinate fasciculus L * Inferior fronto-occipital fasciculus L * Retrolenticular part of internal capsule L | * Sagittal stratum (include inferior longitidinal fasciculus and inferior fronto-occipital fasciculus) L * External capsule L | |  |
| **278** | **-49, -4, 19** | * Superior longitudinal fasciculus L |  | |  |
| **Radial Diffusivity**  **A-Carriers**  0.00055±  0.000072  **GG homozygotes**  0.000539±  0.000073 | | **37377** | **-25, 34, -2** | * Anterior corona radiata L * Inferior fronto-occipital fasciculus L * Uncinate fasciculus L * Retrolenticular part of internal capsule L * Superior longitudinal fasciculus (temporal part) L * Posterior thalamic radiation (include optic radiation) L * Inferior longitudinal fasciculus R * Inferior longitudinal fasciculus L * Posterior thalamic radiation (include optic radiation) R * Retrolenticular part of internal capsule R, External capsule R * Inferior fronto-occipital fasciculus R | | * Anterior corona radiata R * Forceps minor, Forceps major * Anterior thalamic radiation R * Anterior corona radiata L * Uncinate fasciculus L * Superior longitudinal fasciculus (temporal part) L * Splenium of corpus callosum * Anterior thalamic radiation R * Genu of corpus callosum, Cingulum (cingulate gyrus) L * Corticospinal tract L and R | Positive Correlation |  | |
| **Mean Diffusivity**  **A-Carriers**  0.000767±  0.000051  **GG homozygotes**  0.000767±  0.000051 | | **41606** | **-14, 33, 12** | * Inferior fronto-occipital fasciculus L * Uncinate fasciculus L * Retrolenticular part of internal capsule L * Superior longitudinal fasciculus (temporal part) L * Posterior thalamic radiation (include optic radiation) L * Inferior longitudinal fasciculus R * Inferior longitudinal fasciculus L * Posterior thalamic radiation (include optic radiation) R * Retrolenticular part of internal capsule R * Corona Radiata L * Corticospinal tract L * Cingulum (cingulate gyrus) L | | * External capsule R * Inferior fronto-occipital fasciculus R * Anterior corona radiata R * Forceps minor, Forceps major * Anterior thalamic radiation R * Anterior corona radiata L, * Uncinate fasciculus L * Superior longitudinal fasciculus (temporal part) L * Splenium of corpus callosum, * Anterior thalamic radiation R * Genu of corpus callosum | Positive correlation |  | |

 **Figure 1 Supp**



**Figure 2 Supp**

**References**

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