SUPPLEMENTARY METHODS

Participants

Participants were drawn from the Edinburgh High Risk Study\(^1\) and were recruited between 1994 and 1999. All subjects in the present study were of Caucasian Scottish ethnicity. Full details of the recruitment process have been described previously\(^1\). All subjects provided written consent and the study was approved by the local research ethics committee. Participants were given a detailed clinical, neuropsychological and brain imaging assessment at baseline and undertook further such assessments at 18 month intervals up until 2004. Psychotic symptoms were assessed using the Present State Examination (PSE-9)\(^2\). Subjects were followed up throughout the course of the study or until they developed schizophrenia. All assessments were therefore made prior to the development of any schizophrenic illness. There was no difference between genotype groups in the length of follow-up, or in age at which psychotic symptoms were first observed.

Genotyping

Genomic DNA was extracted from venous blood samples using standard protocols. Single nucleotide polymorphisms (SNPs) were genotyped by the Wellcome Trust Clinical Research Facility, Edinburgh, using TaqMan assay-by-design assays. Genotyping was performed for four SNPs from the originally defined deCODE core at-risk haplotype (SNP8NRG221132, SNP8NRG221533, SNP8NRG241930, SNP8NRG243177).

For microsatellite genotyping primers for 478B14848 and 420M91395 (sequences taken from the deCODE website) were used to PCR amplify the region
flanking the microsatellite repeats. One of the primers was 5'-modified with the fluorescent dye FAM. Products were analyzed by fragment analysis on an ABI 3730 DNA Analyzer.

The program PHASE version 2.1 was used to assign the deCODE 4 SNP haplotypes to individuals. Haplotypes were assigned where the PHASE estimate was greater than or equal to 0.9.

**Behavioural Task**

Participants performed the verbal initiation section of the Hayling sentence completion test in the MRI scanner, as described previously. Briefly, subjects were shown sentences with the last word missing and were asked to think of an appropriate word to complete the sentence and press a button when they had done so. Sentences were presented for a period of 3 seconds followed by a fixation cross for 2 seconds in blocks of 40 seconds. The rest condition consisted of viewing a screen of white circles on a black background for 40 seconds. Immediately after scanning, subjects were given the same sequence of sentences on paper and requested to complete each sentence with the word they first thought of in the scanner. ‘Word appropriateness’ scores were determined from the word frequency list of sentence completion norms.

**Functional MRI**

MRI scanning data were available for 63 of the 79 participants. Imaging was carried out on a GE 1.5 T Signa scanner (GE Medical, Milwaukee, USA) at the SHEFC Brain Imaging Research Centre, Edinburgh. Axial gradient-echo planar images (EPI) (TR/TE = 4000/40 ms; matrix 64 x 128; FOV 220 x 440 mm) were acquired continually during the experimental paradigm (Hayling task). Thirty eight contiguous
5 mm slices were acquired within each TR period. Each EPI acquisition was run for 204 volumes of which the first 4 volumes were discarded. Visual stimuli were presented using a screen (IFIS, MRI Devices, WI, USA) placed in the bore of the magnet. Scan analysis was performed using SPM2 software (http://www.fil.ion.ucl.ac.uk/spm/). Scans were realigned, normalized, and spatially smoothed with a 6 x 6 x 6 mm$^3$ full-width half maximum (FWHM) Gaussian filter. Statistical analysis was performed using the general linear model approach as implemented in SPM. At the individual subject level sentence completion and rest conditions were modelled separately, each modelled by a boxcar convolved with a synthetic haemodynamic response function. The estimates of the subject’s movement during the scan were also entered as ‘covariates of no interest’. Before fitting the model, a high pass filter (400s cutoff) and correction for autocorrelation were applied to the data. A single contrast was constructed to examine sentence completion conditions versus rest. One contrast image per subject was then entered into a second level random effects analysis (ANOVA) to examine the effects of genotype status (C/C, C/T, and T/T). Statistical maps were thresholded at a level of $P < 0.001$ uncorrected, and regions were considered significant at $P < 0.05$ cluster level corrected for multiple comparisons. All $P$ values quoted are at the corrected cluster level. Co-ordinates were converted from MNI (Montreal Neurological Institute) to Talairach co-ordinates using a non-linear transformation (http://www.mrc-cbu.cam.ac.uk/Imaging).

**Structural MRI**

A structural scan was acquired during the same scanning session as the fMRI. The automated methods applied to the acquisition, pre-processing and analysis of images
have been described in detail previously\textsuperscript{6}. Scanning for volumetric analysis consisted of a three-dimensional magnetisation prepared rapid-acquisition gradient echo sequence consisting of an 180° inversion pulse followed by a fast low angle shot collection (flip angle 12°, TR/TE = 10ms/4ms, TI = 200ms, relaxation delay time 500ms, field of view (FOV) 250mm) giving 128 contiguous 1·88mm thick slices in the coronal plane orthogonal to the Talairach plane. We corrected for any inhomogeneity in the head coil. Voxel-Based Morphometry was performed using the SPM99 toolbox (Wellcome Department of Imaging Neuroscience, London). A study-specific template and a priori probability maps for grey matter, white matter and cerebral spinal fluid were constructed. Using these study specific templates all of the images were spatially normalised and segmented, eliminating large-scale differences between the subjects, using a 12 parameter affine transformation. All of the resulting grey matter segments were then smoothed at 12mm FWHM. Statistical analyses were performed on a voxel by voxel basis using in SPM99, based on the general linear model. The total grey matter as calculated from the native space images was included as nuisance variable. Contrasts were constructed to examine both increased and decreased Grey Matter Density (GMD) between the three genotype groups. In order to attempt to define any differences in GMD between groups, statistical parametric maps were thresholded at $P < 0.01$.

**Statistical Methods**

Non-parametric statistics were conducted using Fisher’s Exact Test. Parametric statistics were conducted using ANOVA and post-hoc group comparisons were made using the Student-Newman-Keuls test for homogenous subsets. We did not perform corrections for multiple testing in our genetic association data as the markers from the
deCODE haplotype are in moderate linkage disequilibrium and the degree of independence between markers is therefore low.


