Supplementary Online Content


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This supplementary material has been provided by the authors to give readers additional information about their work.
eAppendix 1. Methods: Excluded subjects
One patient and one control were excluded before preprocessing because of poor MRI image quality at follow-up, since effects of head motion during the MRI acquisition on gray matter (GM) volume and thickness estimates have been reported. Nine patients were excluded because they did not meet the inclusion criteria at follow-up (diagnosis was changed into psychotic disorder-NOS (3 patients), bipolar disorder (1), major depressive disorder (1), anxiety disorder (1), and 3 patients lacked sufficient diagnostic information at follow-up).

eAppendix 2. Methods: Differences between subjects who participated and who did not
Using our baseline sample (patients, n=162; controls, n=167), we examined differences in demographic and global brain data at baseline between subjects who participated and who did not participate (i.e. who did not take the follow-up assessment) in this study, in patients and controls separately. Demographic variables at baseline include age, gender, handedness, subject and parental education, and IQ for both groups, and duration of illness, PANSS scores (positive, negative, and general subscales scores, and a total score), and GAF score for patients. Global brain data at baseline include the intracranial volume (IC), volumes of total brain (TB), GM and white matter (WM) of the cerebrum, and the lateral ventricle (LV) and third ventricles (V3).

Independent-sample t tests were used to investigate group differences in continuous demographic variables at baseline, and chi-square tests were applied to examine group differences in gender and handedness. Regression was applied to investigate differences in baseline brain measures, controlling for age, gender, and ICV (except when ICV was the dependent variable). A statistical significant threshold of p <.05 was applied.

eAppendix 3. Methods: Antipsychotic medication
To calculate the cumulative dosage of typical antipsychotic medication during the scanning interval, a table from the Dutch National Health Service was used to derive the haloperidol equivalents. For atypical antipsychotic medication, the respective pharmaceutical companies suggested conversion rates into haloperidol equivalents (clozapine, 40:1; olanzapine, 2.5:1; risperidone, 1:1; sulpiride, 170:1; quetiapine, 50:1; and sertindole, 2:1).

eAppendix 4. Methods: MRI parameters
A 3-dimensional (3D), T1-weighted coronal spoiled-gradient echo scan of the whole head (256×256 matrix, echo time [TE]=4.6 ms, repetition time [TR]=30ms, flip angle=30°, 160-180 contiguous slices; 1×1×1.2 mm3 voxels, field of view [FOV]=256mm/70%) was acquired. Furthermore, a single-shot echo planar imaging scan was made as part of a diffusion tensor imaging series (SENSE factor 2.5; flip angle=90°; 60 transverse slices of 2.5 mm; no gap; 128×96 acquisition matrix; FOV=240 mm; TE=78 ms) together with a magnetization transfer imaging scan (60 transverse slices of 2.5 mm; no gap; 128×96 acquisition matrix; FOV=240 mm; flip angle=8°; TE=4.5 ms; TR=37.5 ms).

eAppendix 5. Methods: In-house volumetric processing
At baseline, the T1-weighted images were automatically put into Talairach orientation without scaling, by registering them to a model brain. The two other scans were registered to the T1-weighted image by minimizing a mutual information joint entropy function. The co-registered scans were used for automatic segmentation of the IC, based on histogram analysis and morphology operations. The IC segmentations were visually checked and manually edited where necessary. The follow-up T1 scan was registered to the baseline T1 scan and the baseline IC segment was used as input for the follow-up IC segment, which was also visually checked and manually edited. The intracranial segments served as a mask for the subsequent processing steps. The T1-weighted images were corrected for field inhomogeneities using the N3 algorithm. Our automatic processing pipeline was used for segmentation of TB, GM and WM of the cerebrum. In short, pure GM and WM intensities were directly estimated from the image. The amounts of pure and partial volume voxels were modeled in a nonuniform partial volume density, which is fitted to
the intensity histogram. Expected tissue fractions, based on the pure intensities and the partial volume density, were subsequently computed in each voxel within the cerebrum. TB volume was calculated by adding the GM and WM segments. Binary images of GM and WM were created using 0.5 as a threshold: voxels in the GM partial volume map with a fraction >0.5 were considered as GM, and similarly, voxels in the WM partial volume map with fractions >0.5 were classified as WM. LV and V3 volumes were also assessed. The software included histogram analysis, mathematical morphology operations, and anatomical knowledge-based rules to connect all voxels of interest, as was validated before. The intracranial mask and ventricle and cerebellum segments were checked visually and edited where necessary.

eAppendix 6. Methods: Surface-based cortical processing and volumetric subcortical segmentation in FreeSurfer

To extract reliable cortical and subcortical estimates, images were automatically processed with the longitudinal stream.

The cortical processing stream in FreeSurfer includes a Talairach transformation, removal of non-brain tissue using the T1-weighted image and the intracranial mask, and segmentation of GM/WM tissue. The cortical surface of each hemisphere was inflated to an average spherical surface to locate the pial surface and the GM/WM boundary. Automatic subcortical volumes were delineated using information on image intensity, probabilistic atlas location and spatial relationships between subcortical structures.

Specifically, an unbiased within-subject template space and image was created using robust, inverse consistent registration. Several processing steps, such as skull stripping, Talairach transformation, atlas registration as well as spherical surface maps and parcellations were then initialized with common information from the within-subject template, thereby significantly increasing reliability and statistical power.

eAppendix 7. Methods: Quality check of MRI images and extraction of cortical variables in FreeSurfer

The entire cortex of each image was visually inspected, and any topological defects in GM and WM were corrected manually. Subcortical quality check was performed in accord with ENIGMA protocol (http://enigma.ini.usc.edu). Cortical thickness was computed as the shortest distance between the pial surface and the GM/WM boundary at each point across the cortical mantle. Surface area was quantified by assigning an area to each vertex equal to the average of its surrounding triangles. Cortical volume was calculated by computing the thickness by area of each vertex.
eAppendix 8. Results: Differences between subjects who participated at follow-up measurement and those who did not
There were no significant differences between patients who did and did not participate at follow-up in terms of demographic and global brain variables. Similarly, no significant differences were found between controls who did and did not participate, except for a higher level of education (p=.04) and larger LV (p=.01) in those who participated in the follow-up.

eAppendix 9. Results: The effect of clinical confounders
In case of a significant association between IQ change and change in a brain measure in patients (i.e. LV, global cortical volume and thickness, and local cortical volume, thickness, and surface area), we repeated the analyses and controlled them for PANSS total score, GAF score at follow-up, cannabis use, cumulative antipsychotic medication intake during the interval, duration of illness, or level of education. The correlations between change in IQ and change in brain measures in patients over time did not change materially after controlling for these factors, except that the correlation between IQ change and change in LV showed a trend toward significance after controlling for cumulative antipsychotic medication intake (p=.10).

eAppendix 10. Results: WAIS-subscales
In brain measures which showed a significant association with IQ change (i.e. LV, global cortical volume and thickness, and local cortical measures [volume, thickness, and surface area]) we performed post-hoc analyses to examine correlations between change in IQ subscales (Digit symbol coding [processing speed], Information [verbal comprehension], Arithmetics [working memory], and Block design [perceptual organization]) and change in brain measures in patients. None of the correlations between change in subtest score and change in global brain measures reached significance after correction for multiple comparisons. Locally, change in cortical volume, thickness and surface in small areas in the frontal and temporal cortices, were significantly and positively correlated with change in some of the IQ subtest scores. On average, these correlations were much less pronounced than the correlation with estimated total IQ and change in these cortical measures (see Supplementary eFigure 1).

eAppendix 11. Results: Subgroup analyses
Based on the significant association between IQ change and cortical thickness change in patients, we performed post-hoc analyses to identify whether patients who showed both excessive cortical thinning and loss in IQ differed from those who displayed increases in IQ and cortical thickness. A total of 21 patients showed IQ decline as well as cortical thinning, while 10 patients displayed increases in both IQ and cortical thickness. We compared these subgroups on level of education (both of the subjects themselves and their parents), duration of illness, positive, negative and general PANSS symptom scores at follow-up, GAF score at follow-up, and antipsychotic medication intake (haloperidol equivalent) during the interval. In the subgroup with IQ loss in combination with cortical thinning, subject education level was significantly lower (p=.03), PANSS negative symptom score significantly higher (p=.02), and GAF score significantly lower (p=.003) than the group who showed increases in cortical thickness and IQ.
eFigure. Statistical maps showing regions of cortical change (left: volume; middle: thickness; right: surface area) significantly correlated with change in IQ subscales in patients: (a) Digit symbol coding, (b) Information, (c) Arithmetics, and (d) Block design.

n=78. For each hemisphere the lateral and medial views are shown. Hot colours indicate a positive correlation (p<0.0125 [0.05/4 IQ subscales], clusterwise correction; controlled for age and gender).
eTable. Demographic and clinical information of patients and controls
p-values with statistical significance are shown in boldface.

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controls

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**eReferences**


