Table S1. Modularity in patients with schizophrenia and healthy controls

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Modules in healthy controls** | | | | |
| Module 1 | Module 2 | Module 3 | Module 4 | Module 5 |
| Precentral\_L  Precentral\_R  Frontal\_Sup\_L  Frontal\_Sup\_R  Frontal\_Sup\_Orb\_L  Frontal\_Sup\_Orb\_R  Frontal\_Mid\_L  Frontal\_Mid\_R  Frontal\_Mid\_Orb\_L  Frontal\_Inf\_Oper\_L  Frontal\_Inf\_Oper\_R  Frontal\_Inf\_Tri\_L  Frontal\_Inf\_Tri\_R  Frontal\_Inf\_Orb\_L  Frontal\_Inf\_Orb\_R  Rolandic\_Oper\_L  Rolandic\_Oper\_R  Supp\_Motor\_Area\_L  Supp\_Motor\_Area\_R  Frontal\_Sup\_Medial\_L  Frontal\_Sup\_Medial\_R  Frontal\_Med\_Orb\_L  Insula\_L  Insula\_R  Cingulum\_Ant\_L  Cingulum\_Ant\_R  Cingulum\_Mid\_L  Cingulum\_Mid\_R  Lingual\_L  Parietal\_Sup\_R  Paracentral\_Lobule\_L  Paracentral\_Lobule\_R  Heschl\_L  Heschl\_R  Temporal\_Sup\_L | Olfactory\_L  Olfactory\_R  Frontal\_Med\_Orb\_R  Rectus\_L  Rectus\_R  Hippocampus\_L  Hippocampus\_R  ParaHippocampal\_L  ParaHippocampal\_R  Amygdala\_L  Amygdala\_R  Fusiform\_L  Fusiform\_R  Caudate\_L  Caudate\_R  Temporal\_Pole\_Sup\_L  Temporal\_Pole\_Sup\_R  Temporal\_Mid\_L  Temporal\_Mid\_R  Temporal\_Pole\_Mid\_L  Temporal\_Pole\_Mid\_R  Temporal\_Inf\_L  Temporal\_Inf\_R | Calcarine\_L  Calcarine\_R  Cuneus\_L  Cuneus\_R  Lingual\_R  Occipital\_Sup\_L  Occipital\_Sup\_R | Frontal\_Mid\_Orb\_R  Cingulum\_Post\_L  Cingulum\_Post\_R  Occipital\_Mid\_L  Occipital\_Mid\_R  Occipital\_Inf\_L  Occipital\_Inf\_R  Postcentral\_L  Postcentral\_R  Parietal\_Sup\_L  Parietal\_Inf\_L  Parietal\_Inf\_R  SupraMarginal\_L  SupraMarginal\_R  Angular\_L  Angular\_R  Precuneus\_L  Precuneus\_R  Temporal\_Sup\_R | Putamen\_L  Putamen\_R  Pallidum\_L  Pallidum\_R  Thalamus\_L  Thalamus\_R |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Modules in patients with schizophrenia** | | | | | | |
| Module 1 | Module 2 | Module 3 | Module 4 | Module 5 | Module 6 | Module 7 |
| Frontal\_Inf\_Oper\_L  Frontal\_Inf\_Oper\_R  Frontal\_Inf\_Tri\_L  Frontal\_Inf\_Tri\_R  Frontal\_Inf\_Orb\_L  Rolandic\_Oper\_L  Rolandic\_Oper\_R  Frontal\_Sup\_Medial\_L  Cingulum\_Post\_L  Cingulum\_Post\_R  Occipital\_Mid\_L  Occipital\_Inf\_L  Fusiform\_L  Postcentral\_L  Postcentral\_R  Parietal\_Inf\_L  Parietal\_Inf\_R  SupraMarginal\_L  SupraMarginal\_R  Angular\_L  Angular\_R  Precuneus\_L  Precuneus\_R  Heschl\_L  Heschl\_R  Temporal\_Sup\_R  Temporal\_Mid\_R  Temporal\_Inf\_L  Temporal\_Inf\_R | Precentral\_L  Precentral\_R  Frontal\_Sup\_L  Frontal\_Sup\_Orb\_R  Frontal\_Mid\_L  Frontal\_Mid\_R  Frontal\_Mid\_Orb\_L  Frontal\_Mid\_Orb\_R  Frontal\_Inf\_Orb\_R  Supp\_Motor\_Area\_L  Frontal\_Sup\_Medial\_R  Frontal\_Med\_Orb\_L  Frontal\_Med\_Orb\_R  Cingulum\_Ant\_R  Cingulum\_Mid\_L  Cingulum\_Mid\_R  Calcarine\_L  Calcarine\_R  Cuneus\_L  Cuneus\_R  Lingual\_L  Lingual\_R  Occipital\_Sup\_L  Occipital\_Sup\_R  Occipital\_Mid\_R  Occipital\_Inf\_R  Fusiform\_R  Paracentral\_Lobule\_L  Paracentral\_Lobule\_R  Temporal\_Sup\_L | Parietal\_Sup\_L  Parietal\_Sup\_R | Caudate\_L  Caudate\_R | Putamen\_L  Putamen\_R  Pallidum\_L  Pallidum\_R | Thalamus\_L  Thalamus\_R | Frontal\_Sup\_R  Frontal\_Sup\_Orb\_L  Supp\_Motor\_Area\_R  Olfactory\_L  Olfactory\_R  Rectus\_L  Rectus\_R  Insula\_L  Insula\_R  Cingulum\_Ant\_L  Hippocampus\_L  Hippocampus\_R  ParaHippocampal\_L  ParaHippocampal\_R  Amygdala\_L  Amygdala\_R  Temporal\_Pole\_Sup\_L  Temporal\_Pole\_Sup\_R  Temporal\_Mid\_L  Temporal\_Pole\_Mid\_L  Temporal\_Pole\_Mid\_R |

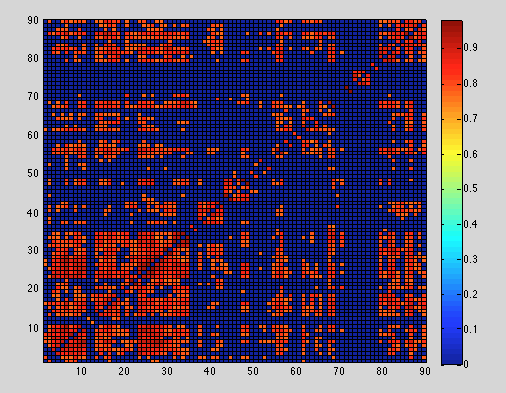
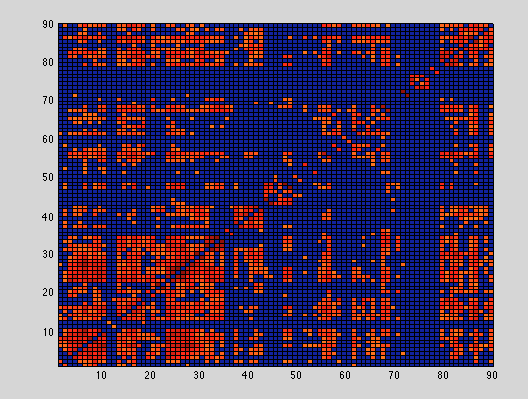
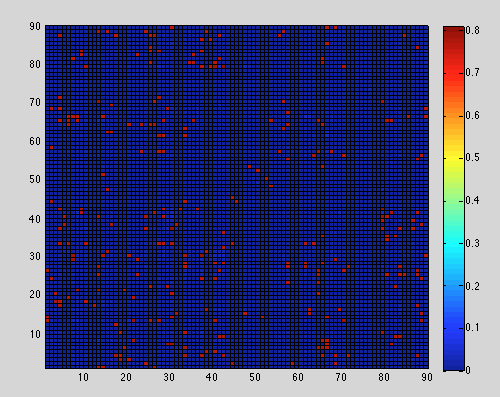
**Supplemental Section: Effect of antipsychotics on topological properties**

A number of observations from experimental animal studies4 and human observational studies from adults with schizophrenia 5–8 have indicated that certain antipsychotics may contribute to progressive loss of brain tissue. The evidence is less conclusive for atypical antipsychotics 7,9. In the current sample, all patients received atypical antipsychotics.

Cumulative exposure to antipsychotics is likely to be more influential on the brain morphology than the current stable dose. In the current study, we did not have the longitudinal information on the exact cumulative dose prescription or intake before the scans. Further, we also lacked any data on the individual concordance levels of the prescribed antipsychotics. Therefore, in line with our previous studies11,12, we approximated the cumulative antipsychotic exposure, using a product of define daily dose (DDD) and duration of illness since the time of first presentation with psychotic episode, determined from patients’ case notes. This index can be taken as an approximate measure of lifetime antipsychotic exposure (ALAE).

We sought to study the relationship between structural covariance and cumulative antipsychotic dose exposure (ALAE) using a liberal threshold of p=0.1, with no correction for multiple testing.

To further delineate the effect of approximate lifetime exposure of antipsychotics on topology of covariance, we constructed two association matrices for patient sample thresholded at minimum density for full connectivity. The first association matrix was obtained without adjusting for the effect of approximate lifetime exposure of antipsychotic dose. The second matrix was obtained after linearly adjusting for the effect of approximate lifetime exposure of antipsychotic dose (i.e. regressing out across-subject differences in ALAE in the patient sample and using residuals to compute 90\*90 correlation matrix). From these two change matrices, we derived a differential matrix (∆r) by subtracting one from the other. Of the 4005 cells (90\*89/2), less than 5% had a difference in coefficients >0.1, suggesting that the effect of lifetime antipsychotic exposure on structural covariance affects a small number of associations.



C

B

A

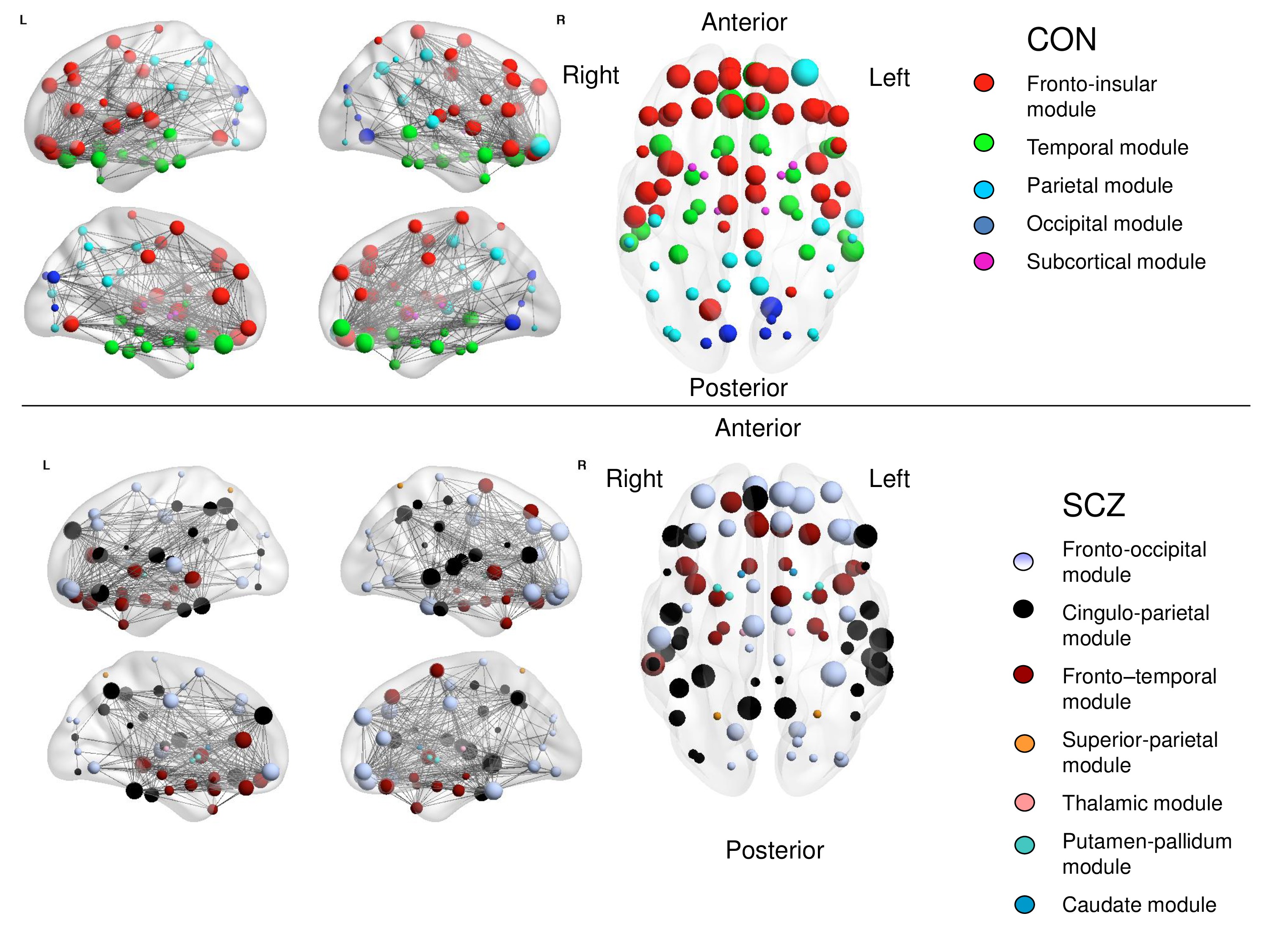
**Figure S1: Effect of approximate lifetime exposure of antipsychotics on topology of covariance:** Correlation matrices for patient sample thresholded at minimum density for full connectivity. A) Association matrix without adjusting for the effect of approximate lifetime exposure of antipsychotic dose. B) Matrix linearly adjusted for the effect of approximate lifetime exposure of antipsychotic dose. Colour bar indicates absolute correlation coefficients (varying from 0 to 1). C) Absolute matrix obtained from subtracting A and B (∆r).

Though a large number of pairwise correlations were relatively unaffected by ALAE, to further clarify if this subtle effect of antipsychotic exposure has indeed any effect on the topological properties of the covariance matrix, we obtained the global network topological measures at the minimum density of full connectivity for both ALAE-adjusted and non-adjusted networks. Comparison of these values using the same permutation approach described in the manuscript did not reveal any significant differences between the two networks for small-worldness, mean global and global efficiency, clustering coefficient, and targeted and random attack metrics (all p>0.39). These comparisons were undertaken without FDR correction to enable detection of even weak effects.

**Table S2: Effect of antipsychotics on topological properties**

|  |  |  |
| --- | --- | --- |
|  | **Network unadjusted for ALAE** | **Network linearly adjusted for ALAE** |
| **Measures of Segregation** | | |
| Clustering Coefficient | 0.7463 | 0.7476 |
| **Measures of Integration** | | |
| Global Efficiency | 0.6176 | 0.6207 |
| **Measures of resilience** | | |
| *Targeted Attack* | | |
| Mean relative size of remaining large component | 37.5% | 36.7% |
| Mean relative global efficiency | 22.3% | 22.2% |
| *Random Attack* | | |
| Mean relative size of remaining large component | 47.9% | 47.8% |
| Mean relative global efficiency | 31.8% | 31.5% |

In summary, the negative results despite our extensive approach to relate available antipsychotic treatment data to covariance of longitudinal changes suggests that the reported topology of covariance is unlikely to be due antipsychotic use. Of note, while a number of rigorous studies have examined the effect of antipsychotics on structural changes in schizophrenia, to our knowledge there are no reports on how cumulative antipsychotic exposure affects the structural covariance among various brain regions in schizophrenia.



**Figure S2: Graphical representation of gray matter connectomes.** Connectomes in controls and schizophrenic patients are visualized using BrainNet viewer ([www.nitrc.org/projects/bnv](http://www.nitrc.org/projects/bnv)). The modules are color-coded separately for each network in the online version of this image. The size of the nodes is proportional to the nodal degree (number of edges) within each connectome.

**Supplemental Section: Voxel Based Morphometric Differences between controls and patients with schizophrenia**

The whole-brain grey matter VBM analyses revealed 13 clusters which were reduced in patients with schizophrenia compared to healthy controls using an uncorrected threshold of *p* < .01 with a cluster extent of 100 voxels. Largest clusters were found in the cingulate gyrus, thalamus, inferior frontal gyrus, insula and hippocampus. Other regions of reduced grey matter were also found in temporal regions, parahippocampal gyrus and also the postcentral gyrus. These results are summarized in Table S3 and Figure S3 below.

**Table S3.** **VBM results for grey matter volume differences between schizophrenia patients and healthy controls** (*p* < .01 (uncorrected), *k*=100).There were no regions with significant tissue increase in patients compared to controls.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Peak region** | **L/R** | **Peak MNI coordinates (mm)** | | | **Cluster extent (voxels)** | **Peak *T value*** |
| **x** | **y** | **z** |
| Middle cingulate gyrus | L | -3 | -33 | 38 | 12284 | 4.51 |
| Thalamus | L | -2 | -15 | 5 | 648 | 3.5 |
| Inferior frontal gyrus | L | -41 | 29 | -6 | 896 | 3.44 |
| Insula | R | 51 | 12 | -2 | 1047 | 3.38 |
| Middle temporal gyrus | L | -53 | -60 | 14 | 345 | 3.38 |
| Superior frontal gyrus | R | 17 | 56 | 24 | 504 | 3.32 |
| Postcentral gyrus | L | -57 | -8 | 33 | 272 | 3.06 |
| Hippocampus | L | -30 | -15 | -17 | 662 | 3.04 |
| Superior temporal gyrus | L | -60 | -2 | 8 | 246 | 2.95 |
| Parahippocampal gyrus | R | 20 | -3 | -29 | 438 | 2.89 |
| Middle temporal gyrus | L | -50 | -59 | -3 | 236 | 2.89 |
| Insula | L | -44 | -11 | 5 | 161 | 2.81 |
| Superior temporal gyrus | R | 56 | -29 | 17 | 162 | 2.75 |



**Figure S3.** **VBM results for grey matter volume differences between healthy controls> schizophrenia patients. For display purposes, regions surviving a threshold of** *p* < .01 and cluster extent of *k*=100 are shown on selected slices of a T1 single subject template using MRICron.

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