Supplementary Methods:

Medications

Medication information was available for twenty-two schizophrenia patients. Medications included; Typical Antipsychotics : haloperidol (5), fluphenazine (3), perphenazine (2), thiothixene (1); Atypical Antipsychotics: risperidone (8), aripiprazole (4), paliperidone (1), quetiapine (1), olanzapine (1). SSRI's /SNRI's: fluoxetine (2), paroxetine (2), citalopram (2), escitalopram (2), venlafaxine (2), duloxetine (1); Tricyclic Antidepressants : amitriptyline (3), impramine (1); Atypical antidepressants; buproprion (2), trazodone (3); Mood Stabilizers: divalproex (4), oxycarbazepine (3), lamotrigine (2), gabapentin (1), topiramate (2); Benzodiazepines: clonazepam (6), lorazepam (2), diazepam (1); Anticholinergics: benztropine (6); Non- Benzodiazepine Hypnotics: zolpidem (2).

Preprocessing

Preprocessing of resting state data generally followed the approach of (30, 39). The first 5 images were discarded, data were motion corrected using SPM2 (http://www.fil.ion.ucl.ac.uk/spm/), the remaining data were band-pass filtered to remove signal of frequencies higher than 0.1 Hz and lower than 0.005. Resting state images were smoothed using a Gaussian filter of FWHM 4mm and resampled to a resolution of 4x4x4 mm^3.

Tensor calculations and tractography was performed using the DtiStudio software package (37). Fiber tracts were detected using fiber assignment by the continuous tracking (FACT) algorithm (58) with stopping criteria of FA < 0.25 and turning angle of 70 degrees. Since the acquisition resolution for DTI was different than for resting data, all DTI processing was performed in native DTI resolution, the reduced resolution was used only in the final step of creating the gray matter connectivity matrix.

Each subject's anatomical image was co registered to standard MNI (38) space. Each brain was segmented using SPM2 into white matter, gray matter and CSF. An average gray matter mask was created to include 6000 voxels that showed most overlap between subjects and was later used to create 6000x6000 voxel pair connectivity matrices for both resting connectivity and DTI based anatomical connectivity estimates.

Resting State Data Connectivity Matrix

The mean intensity for gray and white matter and CSF, as well as the 6 parameters of motion estimate were removed from the data by Gram-Schmidt orthogonalization as in (39) . The correlation between time courses was calculated for all 6000×6000 voxel pairs within gray matter. The final resting correlation map was transformed to a Z-distribution using Fisher's transform. The distribution was fitted to a Gaussian and adjusted to a zero-centered normal distribution with standard deviation of 1, as in (40, 41). The distribution was fitted to a Gaussian and adjusted to a zero-centered normal distribution with standard deviation of 1, as in (40, 41). This step was done to minimize global intersubject variance. The shift and scaling parameters used in this step showed no significance difference between groups. This final fit was not applied to the analysis of global effect, or in calculation of global mean of connectivity matrix, as it would remove all between group effects.

DTI Data Connectivity Matrix

To quantify the strength of anatomical connectivity between any two WM voxels, we counted all tracts connecting them identified during the tractography step. This created a first order matrix of direct connectivity. Multiplying this matrix by itself creates a second matrix that counts all possible paths that can be built using two connected tracts. Further multiplications yields matrices counting any longer paths. The final outcome was calculated by summing the number of paths of each length (up to N=8 segments) with a weighting that heavily penalized more indirect paths. The connectivity measure $C_{DTI}(x,y)$, for any given voxel pair was then defined as the sum of contributions from all path lengths:

$$C_{DTI}(x,y) = \sum_{i=1:N} 2^{(-N)}\log(1+C_i(x,y)) ,$$

where C_i is number of paths of length connecting voxels x and y.

This DTI connectivity matrix was estimated for WM. Connectivity between gray matter voxels was calculated from the WM connectivity matrix by averaging the values obtained for the nearest gray matter neighbors of each WM voxel. This gave an anatomical connectivity matrix for the same 6000 gray matter voxels used for calculation of resting connectivity.

Spatial Correlation between Structural (DTI) and Functional (resting) Connectivity Matrices

Both resting state correlation and fiber tracking integration techniques outlined above tend to be unreliable for proximate voxels (resting correlations because of smoothing originating both from fMRI scanner and from postprocessing of DTI, (because of the technique used here to propagate connectivity from WM voxels to proximate gray matter voxels). We excluded all voxel pairs located closer than 24 mm from the analysis. Even for larger distances, both measures decreased with increasing distance and thus showed strong negative correlation with distance. To eliminated this trivial similarity between connectivity matrices, the spatial correlation between full 6000x6000 matrices (or between theirs subsets) was calculated using the partial correlation coefficient with the intervoxel distance removed as in (5).

Thus the degree of coherence between anatomical and functional connectivity matrices was quantified by calculating the spatial partial correlation between connectivity matrices (containing estimates of connectivity for all voxel pairs separated by more than 24 mm). To account for the fact that both connectivity measures are strongly correlated to spatial distance separating voxels the spatial distance was removed by using partial correlation.

Supplementary Table

ROI name	X=	Y=	Z=	Size (cc)
Angular Gyrus L	-46	-62	36	8.3
Angular Gyrus R	45	-60	37	9.3
Cingulate Anterior Dorsal	1	28	28	6.5
Cingulate Anterior Ventral	0	33	4	4.5
Cingulate Posterior	0	-47	33	3.8
Cingulate Middle	0	-22	45	10.0
Cuneus	5	-77	26	9.8
Inferior Frontal Gyrus L	-45	22	12	15.8
Inferior Frontal Gyrus R	45	22	12	14.9
Inferior Parietal Lobule L	-52	-43	39	8.3
Inferior Parietal Lobule R	50	-42	38	6.1
Insula L	-40	-5	3	12.6
Insula R	40	-7	4	13.2
Lingual Gyrus	5	-70	-1	8.3
Middle Frontal Gyrus L	-35	33	31	20.0
Middle Frontal Gyrus R	34	31	32	18.0
Medial Occipital Frontal Gyrus L	-44	-76	4	6.6
Medial Occipital Frontal Gyrus R	44	-77	4	6.6
Middle Temporal Gurus L	-53	-47	5	15.8
Middle Temporal Gyrus R	53	-50	6	13.0
Medial Frontal Gyrus (ventral)	1	36	19	12.5
Medial Frontal Gyrus (dorsal)	-2	32	34	12.7
Postcentral L	-54	-25	36	88.3
Postcentral R	54	-26	35	5.4
Precuneus	2	-62	50	9.3
Superior Temporal Gyrus L	-54	-22	8	5.2
Superior Temporal Gyrus R	54	-20	8	5.3
Thalamus	0	-21	5	4.7

Table 1 Supplementary

The anatomically defined regions with corresponding Talairach coordinates of centers and sizes.

***IN THIS ISSUE Statement**

Schizophrenia is hypothesized to involve disordered connectivity between brain regions. Skudlarski et al. (paged xxx-xxx) combined two imaging techniques to measure two different aspects of brain connectivity. Diffusion Tensor Imaging was used to measure strength of anatomical connections, while Resting State temporal correlations quantified the functional connectivity. Schizophrenia patients showed overall deterioration of anatomical connectivity, complex changes in functional connectivity, and decoupling between both measures.