Supplementary Data

Additional Analyses on Group Differences in Brain Functional Organization

In the present study, we used a convenience sample comprising previously collected data without prior coordination of acquisition parameters (i.e., different TRs). In addition, head motion was suggested to have a significant impact on resting-state brain functional connectivity (Saad et al., 2009; Satterthwaite et al., 2012; Van Dijk et al., 2012). We carefully conducted 2-level head motion correction and excluded patients who had head motion greater than the threshold (i.e., SSD = 0.2 mm). To mitigate the bias of different TRs and the impact of head motion on correlations, we performed analyses on nine patients and nine control subjects with the same time length of fMRI data and with minimal motion contamination, for which the findings are reported in the article.

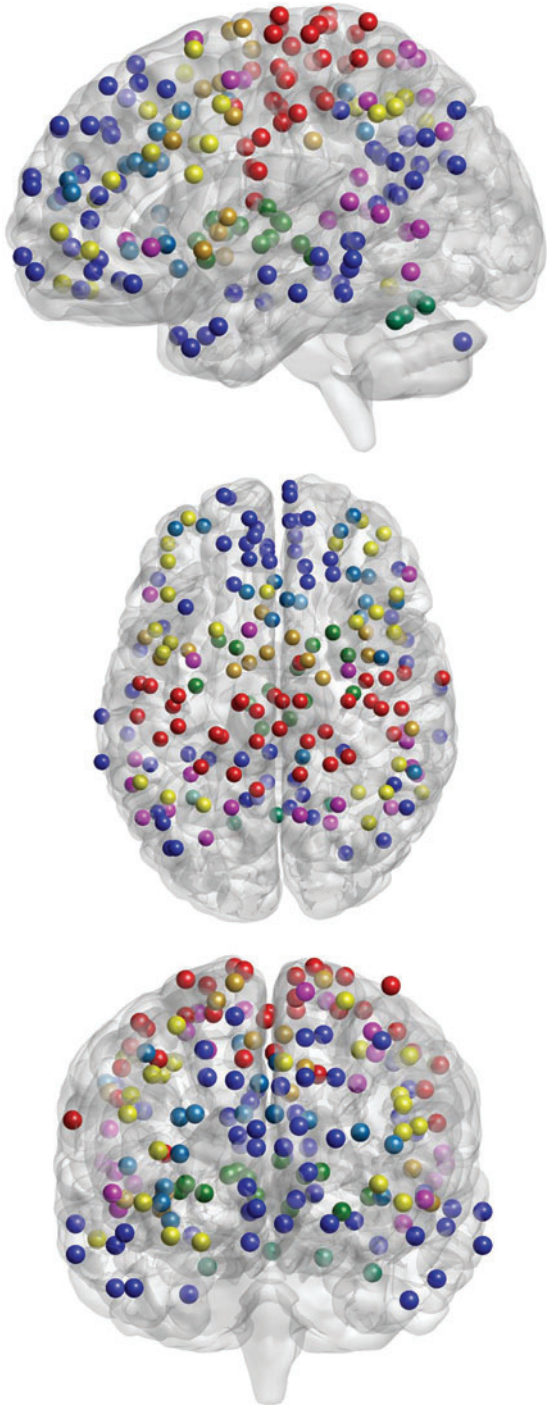
To further test our method in a relatively larger sample, we added another 4 epilepsy patients and 4 age- and motion-matched control subjects to the study group and applied the same method and analyses on 13 epilepsy patients versus 13 control subjects (Supplementary Table S3).

There was no significant group difference in age (two-sample *t*-test, one-tail, *p*-value = 0.42) or gender (9 F/4M in both groups) between the two groups. Each patient and the age-matched control subject had the same number of time points of fMRI data with variation in total time length after correction for motion. The epilepsy patient group had average motion SSD of 0.055 ± 0.020 mm and the healthy control group had average motion SSD of 0.047 ± 0.015 mm. There was no significant group difference in head motion between the two groups (two-sample *t*-test, one-tail, *p*-value = 0.13).

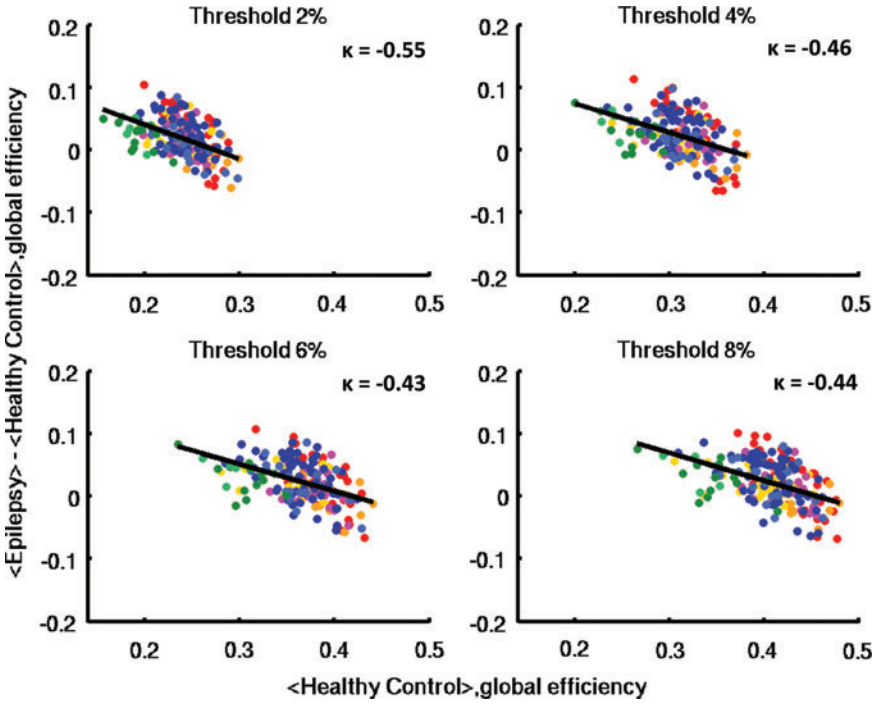
Consistent with the main findings from 9 epilepsy and 9 age-matched control subjects, we observed that regardless of the factors of age of seizure onset, seizure location, and duration of illness, at the whole-brain level, the epilepsy patients showed consistent decreases in local efficiency (i.e., a measure of functional segregation; Supplementary Fig. S5) and increases in global efficiency (i.e., a measure of functional integration; Supplementary Fig. S6) relative to the control subjects.

We again observed a negative hub disruption index in local efficiency examined at the regional level across different functional networks, indicating an exchange of higher efficiency regions to lower efficiency regions (Supplementary Fig. S7). Within the default mode network (DMN), the posterior cingulate cortex (PCC) consistently showed increased local efficiency, while the medial temporal lobe showed decreased local efficiency in the epilepsy group relative to the control group (Supplementary Fig. S7).

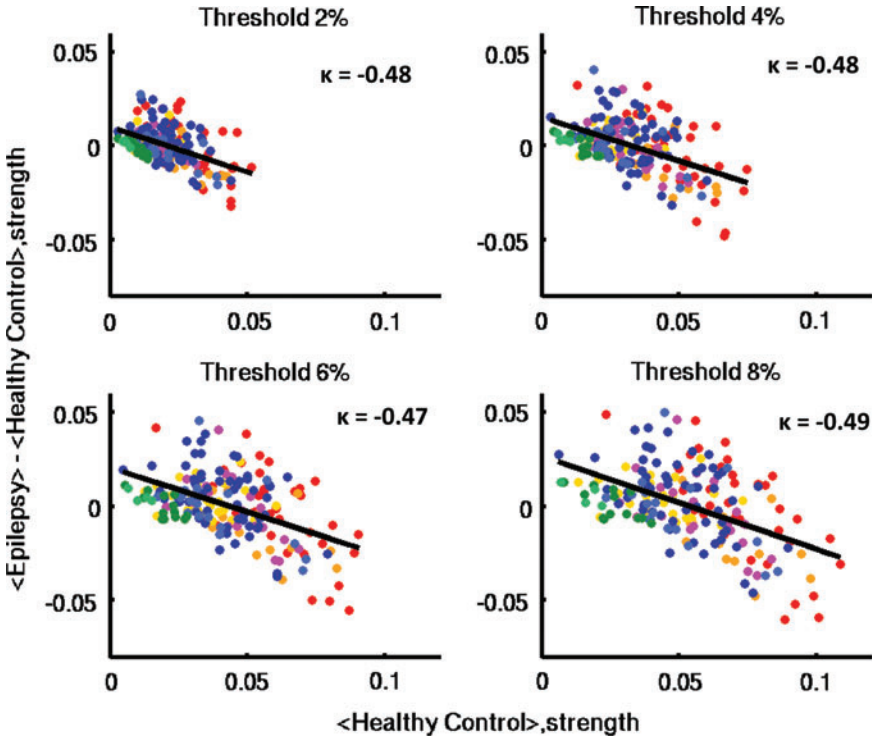
Functional strength at the whole-brain level was statistically similar between the two groups (Supplementary Fig. S8).



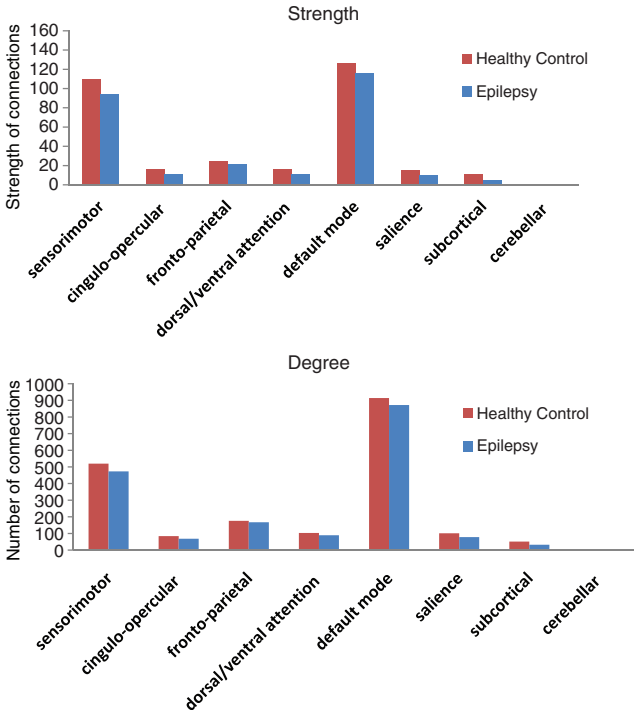
SUPPLEMENTARY FIG. S1. Illustration of the 187 ROIs from sagittal (top), axial (middle), and coronal (bottom) views. ROIs within each functional network are color coded. Functional networks include the sensorimotor (red; 35 regions), cingulo-opercular task control (orange; 14 regions), frontoparietal task control (gold; 25 regions), dorsal/ventral attention (magenta, 20 regions), default mode network (DMN; medium blue, 58 regions), salience network (royal blue; 18 regions), and subcortical/cerebellar (green; 17 regions) network.



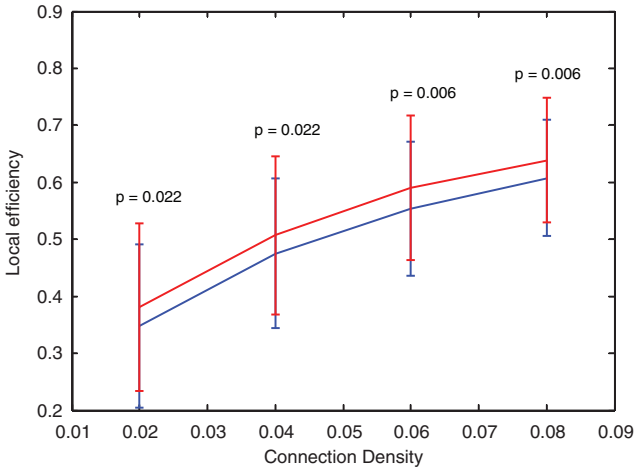
SUPPLEMENTARY FIG. S2. Hub disruption index of global efficiency. The hub disruption index of global efficiency is plotted at each threshold of connection density. Each data point is color coded representing a node belonging to a particular functional network (i.e., red dots represent nodes belonging to the sensorimotor network, and blue dots represent nodes belonging to the default mode network [DMN]). The mean value of global efficiency of each node in the healthy control group <Healthy Control> (*x*-axis) is plotted against the difference between groups in mean global efficiency of each node <Epilepsy> - <Healthy Control> (*y*-axis). The hub disruption index of global efficiency is estimated as the slope of the solid black line fitted to the scatter plots. Negative hub disruption indices are observed across different thresholds, indicating an overall disruption of global efficiency in the epilepsy group.



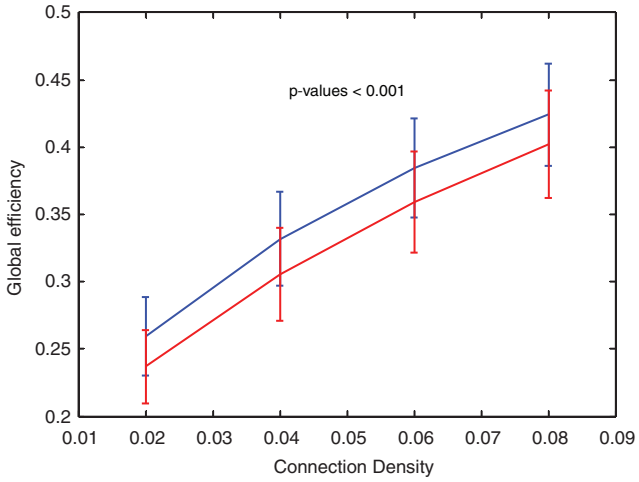
SUPPLEMENTARY FIG. S3. Hub disruption index of strength. The hub disruption index of strength is plotted at each threshold of connection density. Each data point is color coded representing a node belonging to a particular functional network (i.e., red dots represent nodes belonging to the sensorimotor network, and blue dots represent nodes belonging to the DMN). The mean value of nodal strength in the healthy control group <healthy Control> (*x*-axis) is plotted against the difference between groups in the mean nodal strength <Epilepsy> - <Healthy Control> (*y*-axis). The hub disruption index of strength is estimated as the slope of the solid black line fitted to the scatter plots. Negative hub disruption indices are observed across different thresholds, indicating an overall disruption of connection strength in the epilepsy group.



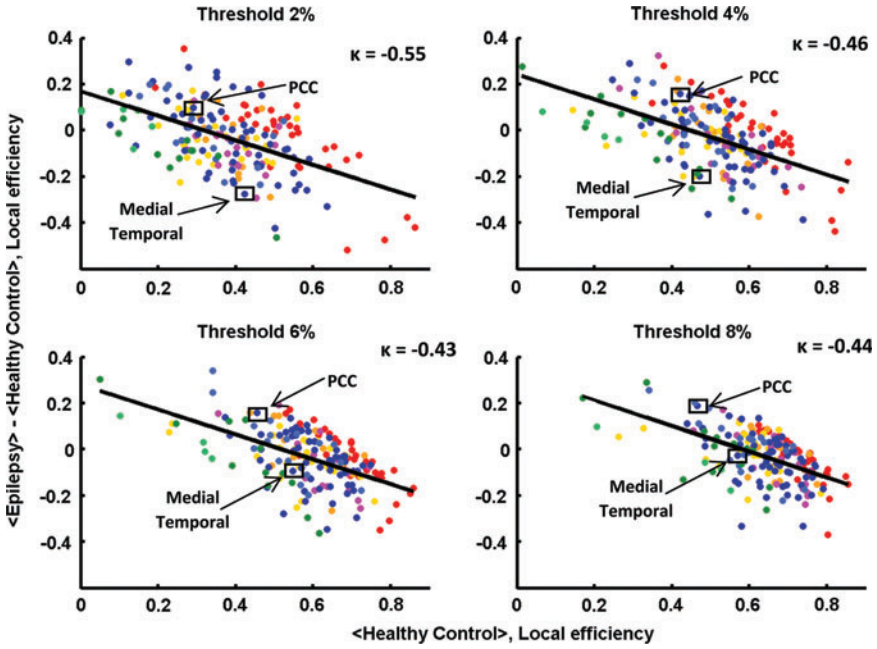
SUPPLEMENTARY FIG. S4. Strength and degree of within-network functional connections. Within each functional network, both groups had statistically similar strength and degree of connections (Binomial proportion test, p-values >0.05 after multiple comparison correction).



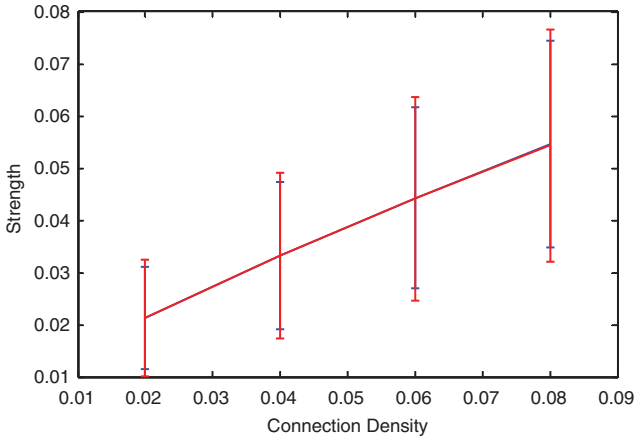
SUPPLEMENTARY FIG. S5. Local efficiency compared between 13 epilepsy and 13 healthy control subjects. The epilepsy patients show significantly decreased local efficiency across a range of different connection densities (p-values listed are corrected for multiple comparisons, Wilcoxon rank sum tests.) (Epilepsy-blue line, Healthy control-red line).



SUPPLEMENTARY FIG. S6. Global efficiency compared between 13 epilepsy and 13 healthy control subjects. Global efficiency is significantly increased in the epilepsy group across a range of different connection densities (Wilcoxon rank sum tests, p-values < 0.001 with multiple comparison correction) (Epilepsy-blue line, Healthy control-red line).



SUPPLEMENTARY FIG. S7. Hub disruption index of local efficiency. The hub disruption index of local efficiency is plotted at each threshold of connection density. The mean value of local efficiency of each node in the healthy control group <Healthy Control> (x-axis) is plotted against the difference between groups in mean local efficiency of each node <Epilepsy> - <Healthy Control> (y-axis). The hub disruption index of local efficiency is then estimated as the slope of the solid black line fitted to the scatter plots. Negative hub disruption indices are observed across different thresholds, indicating an overall disruption of local efficiency in the epilepsy group. Compared with the healthy control group, epilepsy patients show a distinct pattern of regional changes in local efficiency. The posterior cingulate cortex (PCC) has increased local efficiency, whereas the medial temporal lobe shows decreased local efficiency.



SUPPLEMENTARY FIG. S8. Connection strength compared between 13 epilepsy and 13 healthy control subjects. Functional connection strength is statistically similar between epilepsy and healthy control subjects across a range of different connection densities (Wilcoxon rank sum tests, p-values >0.05) (Epilepsy-blue line, Healthy control-red line).

Supplementary Table S1. Characteristics of Epilepsy Patients

Patient number	*Age at study participation (years)*	*Gender*	*Seizure side*	*Seizure location (EEG)*	*Start of syndrome*	*Medications*
1	25	F	L	Status post amygdala/ tumor resection	8–9 years old	Keppra 1500 mg BID, Carbamazepine 200mgBID
2	26	F	R	Mesial temporal onset	Reportedly encephalitis at 3 years old leading to seizure disorders	Lamotrigine 300 mg QAM/QPM, Topiramate 100 mg QAM/200 mg QPM
3	27	F		No definite epileptiform abnormalities on EEG. EEG video suggests an area of neurophysiological dysfunction in the left occipital lobe	17 years old	None at time of fMRI (Previous were zonisamide, levetiracetam, lamotrigine and carbamazepine)
4	28	F	L	Anterior temporal lobe/ mesial temporal sclerosis	14 years old; generalized tonic-clonic	Zonisamide 300 mg, Carbamazepine 500mgBID
5	31	F		Rare left temporal disorganization, which has an uncertain clinical significance. There are certainly no frank epileptiform abnormalities present	7th–8th grade	Lamotrigine, Citalopram
6	33	M	R	Centroparietal region/ parasagittal region	Early teens	Oxcarbazepine 1800 mg/ 600 mg, Keppra 1000 mg/ 2000mg
7	37	F	R	Mesial temporal lobe	31 years old	Keppra 1500mgBID, Zonisamide200mgQAM/ 400QPM
8	44	M	L	Status post temporal cavernoma resection; partial temporal lobectomy	Staring spells as a child and had trouble in school because of it	Lamotrigine 100 mgBID, levetiracetam 1500 mgBID, topiramate 200 mgBID, Nortryptyline 25mgPRN migraines
9	53	M	L	Focal temporal/mesial temporal sclerosis	49 years old	Several medication combinations, including Keppra, lamotrigine, gabapentin, pregabalin, zonisamide, lorazepam

EEG, Electroencephalography.

Supplementary Table S2. Strength of Functional Connections Between Networks

	Proportion of strength in each network	
Functional network	*Healthy control*	*Epilepsy*
Sensorimotor	0.185	0.176
Cingulo-opercular	0.150	0.102
Frontoparietal	0.142	0.149
Dorsal/ventral attention	0.181	0.159
Default mode	0.168	0.230
Salience	0.138	0.128
Subcortical	0.029	0.043
Cerebellar	0.008	0.013

Shown here are the proportions of between-network connection strength in each individual network relative to the total between-network connection strength across all networks in each group. Both groups had similar between-network connection strength (Binomial proportion test, corrected p-values >0.05).

Supplementary Table S3. Characteristics of Four Added Epilepsy Patients

Patient number	*Age at study participation (years)*	*Gender*	*Seizure side*	*Seizure location (EEG)*	*Start of syndrome*	*Medications*
10	19	F	L	Left hemisphere in origin; possibly insular seizure	2 years old	Keppra 1000 mgBID, Zonisamide 300mgQBed, Adderall 30mgAM
11	25	F	L	Mesial temporal onset of seizures	25 years old	Keppra750 mgBID, Lamotrigine200 mgBID, Zonisamide300 mgQBed
12	34	F	L	Temporal region consistent with left mesial temporal sclerosis	Febrile seizures in 1st year of life, complex partial automatisms thereafter, and generalized seizures late in life.	Keppra 1000 mgBID, Carbamazepine 200 mgBID,
13	51	M	L	All seizures electrographically started in the left anterior quadrant	14 months old	Lamotrigine 400 mgBID, Citalopram 60 mg, Levetiracetam 2000 mgBID