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Increased MRI volumetric correlation contralateral to seizure focus in temporal lobe epilepsy

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Abstract

Quantification of volumetric correlation may be sensitive to disease alterations undetected by standard voxel based morphometry (VBM) such as subtle, synchronous alterations in regional volumes, and may provide complementary evidence of the structural impact of temporal lobe epilepsy (TLE) on the brain. The purpose of this study was to quantify differences of regional volumetric correlation in right (RTLE) and left (LTLE) TLE patients compared to healthy controls. A T1 weighted 3T MRI was acquired (1 mm³) in 44 drug resistant unilateral TLE patients (n=26 RTLE, n=18 LTLE) and 44 individually age and gender matched healthy controls. Images were processed using a standard VBM framework and volumetric correlation was calculated across subjects in 90 regions and compared between patients and controls. Results were summarized across hemispheres and region groups. There was increased correlation involving the contralateral homologues of the seizure foci/network in the limbic, subcortical and temporal regions in both RTLE and LTLE. Outside these regions, results implied widespread correlated alterations across several contralateral lobes in LTLE, with more focal changes in RTLE. These findings complement previous volumetric studies in TLE describing more ipsilateral atrophy, by revealing subtle coordinated volumetric changes to identify a more widespread effect of TLE across the brain.

Keywords

epilepsy; gray matter; MRI; networks; volumetric MRI

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Conflict of Interest

None of the authors has any conflict of interest to disclose.

1. Introduction

Temporal lobe epilepsy (TLE) is a common form of epilepsy occurring in adults and is characterized by recurrent temporolimbic seizure activity (Berg et al., 2003; Engel, 2001). A neuropathological hallmark of TLE is atrophy of the epileptogenic (ipsilateral) hippocampus as can be determined from anatomical MRI (Mathern et al., 1995). Volumetric group difference studies employing voxel based morphometry (Ashburner and Friston, 2000) (VBM) have demonstrated widespread gray matter atrophy in TLE compared to healthy controls including hippocampus, neighboring medial temporal, bilateral thalamus, prefrontal, and parietal regions (Bernasconi et al., 2004; Bonilha et al., 2004; Keller et al., 2002b). However, meta-analyses of VBM results in TLE have revealed general inconsistencies in the detection of diffuse gray matter abnormalities compared to controls, with a recent report from Barron et al. concluding ipsilateral hippocampal and bilateral thalamic atrophy were the only reliable findings across studies (Barron et al., 2012; Keller and Roberts, 2008). Some have theorized that damage to the hippocampus and thalamus reflects the original epileptogenic process or predisposition, whereas extrahippocampal atrophy represents secondary mechanisms related to disease progression, such as direct excitotoxic effects of seizure propagation or the deafferentation of distant neurons with synaptic connections to epileptogenic foci (Coan et al., 2014; Keller et al., 2002a; Mueller et al., 2009). Discrepancies in the volumetric literature may reflect the fact that extrahippocampal/temporal abnormalities are heterogeneous across TLE patients and/or are too subtle to consistently detect in standard tests of difference compared to controls.

Morphological correlation presents an alternative methodology to interrogate the structural effects of TLE. In this type of analysis, measures such as gray matter volumes or thickness of two regions are correlated across a group of subjects, providing a measure of the degree to which two regions change together across the group. A strong relationship between structures is thought to indicate coordinated or synchronized structural change as result of genetic or environmental factors, or as a result of disease. Evidence suggests that some structural correlation networks are related to particular behavioral and cognitive systems and also demonstrate overlap with resting state networks determined by functional MRI (Alexander-Bloch et al., 2013). Volumetric correlation analysis may be sensitive to effects undetected by standard VBM comparisons such as subtle, synchronous alterations in regional volumes and may provide complementary evidence of the structural impact of TLE. Furthermore, correlation analysis may elucidate potential relationships between the extratemporal structures with inconsistently reported changes in previous research. While altered cortical thickness networks have been reported (Bernhardt et al., 2011; Raj et al., 2010), volumetric correlation studies of large scale networks in TLE are few (Yasuda et al., 2015). The purpose of this study was to quantify differences of regional volumetric correlation in right (RTLE) and left (LTLE) sided TLE patients compared to healthy controls, similar to methods applied in previous studies (Bernhardt et al., 2014; Hosseini et al., 2012; Kim et al., 2014; Montembeault et al., 2015; Yasuda et al., 2015). Specifically, we aim to assess patterns of alteration involving the regions of each hemisphere and in defined regional groups in RTLE and LTLE.

2. Materials and Methods

2.1 Subjects

The patient cohort consisted of 44 drug resistant temporal lobe epilepsy patients separated into a RTLE group (n=26) and a LTLE group (n=18). Patients were selected from an ongoing study looking at unilateral refractory TLE patients and a similar prior study. All patients were recruited while undergoing presurgical workup for either a selective amygdalohippocampectomy or standard temporal lobectomy and all were recommended for resective surgery by a multidisciplinary panel. The clinically homogenous group of patients was selected based on an inclusion criteria of (1) unilateral TLE determined by standard noninvasive evaluation including ictal and interictal electroencephalography (EEG), high resolution structural MRI, unilateral temporal hypometabolism detected by fluoro-deoxyglucose positron emission tomography (FDG-PET) and neuropsychological testing, and (2) no foreign tissue lesions other than mesial temporal sclerosis. Three patients were excluded from the analysis that had MRI abnormalities additional to mesial temporal sclerosis, including lateral temporal and insular encephalomalacia. Control subjects were recruited as part of the two previously mentioned studies intended to represent a normal population for comparison to the patients. The control groups consisted of neurologically healthy adults, age and gender matched to the patient groups such that each patient had a unique, directly matched control subject. The age difference (patient–control) was 0.27 ± 1.76 years in the RTLE matched control group (RCon) and 0.44 ± 1.34 years in the LTLE matched control group (LCon).

2.2 Image Acquisition

Informed consent was obtained per Vanderbilt University Institutional Review Board guidelines. All images were acquired on a Philips Achieva 3T MRI scanner (Philips Healthcare, Best, Netherlands) with either a 32 or 8 channel head coil, used in the ongoing study and prior study, respectively. Each patient-control pair was acquired with the same head coil to account for potential biases introduced from the coil setup. A standard T1 weighted turbo fast-field echo image was acquired (TR/TE = 8.9/4.6 ms, flip angle 8°, matrix = $256 \times 256 \times 150$, 1 mm³).

2.3 Preprocessing

The image volumes were first corrected using a two-step process. This involved a single pass through an N4BiasCorrection filter and then denoising using an adaptive optimized non-local means filter (AONLM) as implemented by the MATLAB based MRI Denoising Package, both with default settings (Manjon et al., 2010; Tustison et al., 2010). The corrected images were segmented into tissue components using SPM12. To normalize the tissue maps into a common space, we implemented the DARTEL approach. DARTEL ranks among the most accurate registration methods available and was used to maximize regional overlap across subjects (Klein et al., 2009). A sample-specific gray matter average template was created from the affine-registered tissue maps and the deformation information for each subject was used to optimally modulate and warp (normalize) the native gray matter maps to MNI space (Ashburner, 2007). Modulation preserves local amounts of gray matter by scaling the intensity values at each voxel as tissue is expanded or compressed to match the

template (e.g. reduced intensity with greater expansion). The normalized and modulated gray matter intensity maps served as the final processed images for the structural correlation analysis. Visual quality inspection of all data was performed after each preprocessing step. Next, a high resolution Automated Anatomical Labeling (AAL) atlas was resampled to match the normalized gray matter maps (Tzourio-Mazoyer et al., 2002). The coordinates from 90 AAL regions (excluding cerebellar regions) were used to extract the sum of intensity values within each region, which represented each regional volume of gray matter.

2.4 Correlation Matrices

The regional volume values were first detrended by linear regression with three nuisance covariates: total gray matter volume, age, and age². The residual values were used to construct a 90 × 90 cross correlation matrix across each group (RTLE, LTLE, RCon and LCon), using Spearman rank correlation to account for nonlinear relationships of regional volumes. The *r* values were then converted to *z* values using Fisher's *z* transform (Fisher, 1915). The resultant matrices consisted of *z* values for each region pair.

Difference matrices were constructed using the following formula, true *z* difference = (TLE *z* – Con *z*) / (2/(N-3)) where N = the number of subjects. This provided a value at each region pair in units of standard deviations. A nonparametric pair permutation framework with 50,000 iterations was used to estimate null distributions of the difference for each region pair. Iterations involved the creation of two groups by randomly assigning a label of patient or control to each value in a subject pair, calculating the correlation (*z*) for the two random groups, and then calculating a *z* difference using the equation above. This framework took advantage of our paired subject design by ensuring the distribution of age, gender, and coil was the same between the random groups for each iteration. The standard deviation of the null distribution of the 50,000 iterations was computed for each region pair (cell of the matrix). The true *z* difference was then divided by this standard deviation to normalize the *z* differences to compare across region pairs. The normalized *z* difference matrices (RTLE-RCon, LTLE-LCon) were used for subsequent analyses.

2.5 Statistical Comparisons

To assess the overall pattern of alteration in connections between regions of the same hemisphere as well as cross-hemispheric connections, we divided the region pairs into three groups. The ipsilateral hemisphere values (Ipsi) refer to all region pairs where both are in the hemisphere ipsilateral to the seizure focus (n=990), the contralateral hemisphere values (Contra) refer to all region pairs where both are in the contralateral hemisphere (n=990), and the cross hemisphere values (Cross) refer to region pairs where there is one in each of the ipsilateral and contralateral hemispheres (n=2025). We computed the estimated probability density function of *z* difference values of all region pairs within the three subsets of the *z* difference matrices. The x-axis of the curves represents *z* differences in units of normalized standard deviations, while the yaxis represents probability of the specific *z* difference to occur in the sample. In addition, the 2.5% percentile, 50% percentile (median), and the 97.5% percentile value of the *z* difference distribution were computed.

To determine which specific groups of regions contributed most to the hemispheric differences between patient and controls, we divided the 90 regions into twelve region groups (L and R frontal, limbic, occipital, parietal, subcortical, and temporal). The regions included in each region group are given in Supplementary Table 1, and Figure 1 provides a spatial depiction of the group definitions. The frontal, occipital and parietal groups are divided by standard lobar definitions. The subcortical group includes caudate, putamen, pallidum and thalamus. The limbic group includes insula, cingulum, hippocampus, parahippocampus, and amygdala. The temporal group includes the standard temporal lobe regions not included in the limbic group. The same z difference probability curves were created, and the percentiles were computed as above for each region group.

To better understand the relationship between the correlation analysis and the traditional volumetric difference analysis, the regional gray matter volumes for each of the 90 regions were first corrected for head size by calculating the region's percentage of total gray matter volume (the "relative" volume) and then comparing the percentage values between subject groups (RTLE-RCon, LTLE-LCon) using paired T-tests. Statistical significance was considered as $p < 0.01$ and a trend toward significance considered as $p < 0.05$. Note that while similar to traditional voxelwise (VBM) difference analyses, in this case voxel volumes were averaged over the same regions used for the correlation analysis for more direct comparison to the correlation results.

3. Results

The 90×90 z matrices in Figure 2 show the groupwise correlation for RTLE, LTLE, RCon, and LCon groups, in addition to the normalized z difference matrices. The x and y axes correspond to the 90 regions and each colored cell represents a region pair. The matrices are symmetrical about the diagonal, and the values along the diagonal (correlation of a region with itself) were excluded from analysis. The regions are divided and labeled according to region group as denoted by black lines (a list of the region labels can be found in Supplemental Table 1).

Figures 3 and 4 show the estimated probability density distribution curves of the normalized z difference values across the hemisphere or region group. The zero on the x-axis indicates where there is no difference between the patients and controls. The negative x-axis values represent z differences where patients have decreased correlation, while the positive x-axis values indicate pairs where patients have increased correlation compared to controls. The 2.5%, 50% and 97.5% percentile values are given for all analyses in Table 2. For the purposes of reporting the region groups most contributing to the hemispheric differences, we considered 2.5% percentile values less than -2.0 as decreased correlations compared to controls, while increased correlations were indicated by 97.5% percentile values greater than 2.0 .

There were both increases and decreases in correlation among contralateral region pairs in the RTLE patients as indicated by the hemisphere laterality z difference distributions (Figure 3A, Table 2). The increased correlation within the contralateral hemisphere in the patients was shown to involve the temporal (Figure 3B), limbic (Figure 3C) and subcortical region

groups more frequently. The decreased correlation in the RTLE patients within the contralateral hemisphere involved the parietal (Figure 3D), temporal (Figure 3B), frontal and occipital region groups. There was also a decrease in cross hemispheric correlation involving the subcortical region group.

There were increases in correlation among contralateral region pairs in the LTLE patients as indicated by the hemisphere laterality z difference distributions (Figure 4A, Table 2), while there were no hemispheric groups with decreased correlation based on our cutoff of a 2.5% percentile value less than -2.0 . The increased correlation within the contralateral hemisphere in LTLE was shown to involve the limbic (Figure 4B), temporal (Figure 4C), subcortical (Figure 4D), occipital and frontal region groups. Increases in correlation in ipsilateral connections are also seen in the subcortical region group (Figure 4D). The occipital and limbic region groups also were involved in decreased cross hemispheric correlation in LTLE.

The RTLE-RCon volumetric difference analysis indicated a significant decrease in relative gray matter volume in the ipsilateral precentral region ($p=0.0006$, part of the frontal region group), ipsilateral postcentral region ($p=0.0008$, parietal), and ipsilateral paracentral lobule ($p=0.001$, parietal), while a significant increase was found in the contralateral inferior temporal region ($p=0.005$, temporal). There was a trend ($p<0.05$) of relative volumetric decrease in contralateral precentral (frontal), ipsilateral pallidum (subcortical), ipsilateral thalamus (subcortical), and contralateral putamen (subcortical), while there was a trend of relative volume increase in ipsilateral olfactory (frontal), contralateral rolandic operculum (frontal), contralateral olfactory (frontal), contralateral parahippocampal gyrus (limbic) and contralateral fusiform gyrus (occipital).

In the LTLE-LCon difference analysis there was a significant decrease in relative gray matter volume in the ipsilateral inferior parietal region ($p=0.004$, parietal) and ipsilateral hippocampus ($p=0.005$, limbic), while a significant increase was found in the contralateral inferior temporal region ($p=0.002$, temporal). There was a trend of relative volumetric decrease in ipsilateral and contralateral postcentral gyri (parietal) and trend of relative volumetric increase in both the middle and superior divisions of contralateral temporal pole (temporal). These results, as well as the correlation results, are summarized graphically in Figure 5.

4. Discussion

In this study we used regional volumetric correlation to identify structural changes in left and right TLE compared to healthy controls. Changes in correlation were summarized over hemispheres and also across region groups. Overall, the results showed increased correlation within the contralateral hemisphere including the temporal, limbic and subcortical regions in both RTLE and LTLE (Yasuda et al., 2015). In LTLE, there were also increases in correlation involving the contralateral occipital (Yasuda et al., 2015) and frontal regions, as well as the ipsilateral subcortical regions. This more widespread involvement in LTLE is consistent with reports of more widespread structural atrophy in LTLE compared to RTLE (Bonilha et al., 2007; Li et al., 2012; Yasuda et al., 2015). However, this is inconsistent with our findings of fewer regional differences in gray matter volume in the LTLE group than the

RTLE group. This may be due in part to fewer subjects in the LTLE group than RTLE (18 vs. 26).

The increase in volumetric correlation involving the temporal, limbic and subcortical regions within the contralateral hemisphere in both LTLE and RTLE is especially interesting given the ipsilateral homologues of these region include the seizure foci/network in TLE. This is consistent with a report of increased correlations of these regions in a similar study (Yasuda et al., 2015). Increased positive association among regional volumes suggests these homologues undergo mutually trophic changes with other regions in these lobes similarly across patients, creating “networks” of regions not generally related in controls. One possibility is that contralateral region networks experience synchronous, gradual atrophy over the course of the disease and their volumes are positively correlated as a result.

These potential networks have also been observed with methods other than structural imaging as well. In a study using magnetic resonance spectroscopy in TLE, network level coupling of the ratio of N-acetyl aspartate to creatine (NAA/Cr) was found between ipsilateral hippocampus and contralateral subcortical structures (Hetherington et al., 2007). Though not mutually exclusive, another intriguing possibility is that of compensatory mechanisms, potentially to overcome the dysfunction of the ipsilateral epileptogenic regions. Indeed, some research has shown that increased functional connectivity among contralateral temporal regions in TLE patients compared to controls was also related to improvements in working memory (Bettus et al., 2009). Similarly, a study using FDG-PET found a relative increase in glucose metabolism in contralateral mesial and lateral temporal areas compared to controls which was also associated with preserved episodic memory during a Wada test (Trotta et al., 2011). Furthermore, a recent study by Chassoux et al. showed hypermetabolism of contralateral temporal regions in both RTLE and LTLE and was interpreted as a compensatory mechanism which may reflect an inhibitory effect on seizure spread (Chassoux et al., 2016). Our volumetric difference analysis showed, in both RTLE and LTLE, volume of the contralateral inferior temporal region relative to total gray matter volume was increased in patients compared to controls. Taken together with our main finding of increased correlation among contralateral temporal, limbic, and subcortical regions, our results may provide further evidence of compensatory mechanisms in which the volume of gray matter in networks contralateral to the seizure side is preserved or even increased compared to the rest of the brain due to altered functional or metabolic demands.

Decreases in volumetric correlation may reflect selective atrophy of particular regions as a result of seizure excitotoxicity, for instance, such that across a group of patients the normal relationship between the two regions is disrupted. This may be the mechanism behind the decreases involving correlation in contralateral parietal (Bonilha et al., 2006; Coan et al., 2014), temporal, frontal and occipital regions in RTLE. Hence, these interpretations suggest that outside the temporal, limbic and subcortical region groups, there are widespread coordinated changes in LTLE, but focal alterations in RTLE, consistent with a previous study (Bonilha et al., 2007). However, these were not supported by the detection of widespread significant volume changes in LTLE in these region groups. Decreases in cross hemispheric correlation were accompanied in all cases by increases or decreases in

correlation involving the same region groups. This coupling implies that the cross hemispheric decreases are a secondary effect of the within hemispheric changes.

A final noteworthy observation is the general lack of significant ipsilateral limbic and temporal correlation changes for both LTLE and RTLE. It is well known that hippocampal atrophy occurs frequently in TLE and was present in most of our sample (Mathern et al., 1995). Additionally, we found evidence of the expected hippocampal asymmetry in both RTLE and LTLE (Table 1), as well as a significant decrease in relative volume of ipsilateral hippocampus in LTLE compared to controls. Whereas Bonilha et al. found ipsilateral hippocampal volume to be correlated with volumes among both ipsilateral and contralateral regions (Bonilha et al., 2007), our analysis differed in that, instead of looking at relationships with a single region (such as ipsilateral hippocampus), results were summarized across regions groups which included multiple regions. Thus, our results suggest that at the regional group level, mesial temporal atrophy occurs within a structural network in TLE that is similarly correlated in controls, even if the magnitude of volumetric change is greater in patients.

An important distinction to make between volumetric correlation and other measures of correlation, such as functional connectivity, is that each subject contributes a single value (i.e. regional volume) as opposed to a correlation value (i.e. correlation of BOLD signals between two regions over time). The volume values by themselves do not contain information about the level of “connectedness” but are instead correlated across the group. From the groupwise correlation one can only infer group level effects. Thus, one limitation of volumetric correlation measures is that they cannot be directly related to subject level clinical variables such as disease duration, seizure frequency, or measures of cognitive dysfunction. One method to examine the effects of such clinical variables on the correlation is to examine sub-populations (i.e. low disease duration vs. high disease duration). However, the sample size used here limited by our careful age, gender and coil pairing, was not large enough to perform these analyses such that splitting our groups in half ($n=9 \times 2$ for LTLE and $n=13 \times 2$ for RTLE) would have led to a reduced ability to detect a true effect. Another way for future studies to address the association with clinical variables would be to acquire longitudinal T1-weighted images on patients and track subtle volumetric change among networks with corresponding changes in clinical symptoms or comorbidities.

One issue with interpreting difference values is that they can arise from dissimilar sets of correlation values. For example, the correlation of Region A with Region B could be strongly positive in the patient group and near zero in the control group (patient $z = 0.8$, control $z = -0.1$, z difference ≈ 2.5 when $n=18$) or near zero in the patient group and strongly negative in control group (patient $z = 0.1$, control $z = -0.8$, z difference ≈ 2.5 when $n=18$). While both cases demonstrate a significant positive difference, the group correlations may warrant alternative interpretations, thus presenting a limitation to our approach. Some groups have chosen to exclude negative correlation values in similar analyses (Fan et al., 2011; Hosseini et al., 2013) but this procedure discards potentially relevant information by creating an arbitrary cutoff at zero. Another approach is to take the absolute value of the r values (Bernhardt et al., 2011), but this too is problematic when looking at differences in correlation since all emphasis is placed on the strength of correlation rather than

directionality. It is important to note that while the underlying mechanisms for negative volumetric correlation are poorly understood, these relationships are still found in the literature (Bohbot et al., 2007) and could be indicative of inhibitory or competitive processes. For these reasons, we chose to report both negative and positive correlations and differences.

Another limitation of this whole brain, exploratory analysis is the issue of multiple comparisons. Using a maximal statistic family wise error (FWE) correction, none of the differences of an individual region pair in either z difference matrix reached statistical significance of $p < 0.05$ (Nichols and Holmes, 2002). We chose to normalize each region pair difference using the permutation method and to demonstrate trends across hemispheres and regional groups of the brain, despite the reduced confidence we may have about any specific region pair difference. These normalization factors were 1.07 ± 0.13 (mean $\pm$ std dev) across all region pairs in RTLE and 1.11 ± 0.17 in LTLE, illustrating the differences between the null distributions and therefore, the value of the normalization.

A final potential limitation of the study was the choice of parcellation method. We selected the 90 regions as defined by the AAL atlas to corroborate with several other studies that employed a similar method (Fan et al., 2011; Hosseini et al., 2012). However, at the parcellation scale of some AAL regions (e.g. large frontal regions), summing voxel values across a region may miss subtle differences within the region (Bernhardt et al., 2015).

5. Conclusions

This study provides a novel whole brain assessment of volumetric correlation in TLE patients compared to healthy controls, while minimizing the effects of age, gender, head size and MRI head coil. Large scale increases in correlation involving regions contralateral to the seizure network were detected in both LTLE and RTLE, suggesting coordinated volumetric changes of these regions with other contralateral regions not normally related in healthy controls. Outside these regions, results implied widespread correlated alterations across several contralateral lobes in LTLE, with more focal changes in RTLE. The fact that widespread significant volumetric differences between groups were not generally detected using the paired T-tests implies that the correlation analysis detects subtle coordinated volumetric changes across predominantly contralateral regions in both RTLE and LTLE. While contralateral volumetric differences are less frequently reported (Keller and Roberts, 2008), contralateral functional connectivity (Bettus et al., 2010; Bettus et al., 2009; Haneef et al., 2014), volumetric correlation (Bonilha et al., 2007), coordinated neuronal injury measured by MRI spectroscopy (Hetherington et al., 2007), and hypermetabolism of contralateral regions from FDG-PET (Chassoux et al., 2016; Trotta et al., 2011) have been observed in TLE. Further work is needed to understand how alterations in volumetric correlation relate to subject-level disease processes and cognition, as well as to other measures of connectivity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Regional volumetric correlation was compared between TLE and healthy controls.
- There was increased correlation in regions contralateral to seizure focus in TLE.
- In left TLE there were widespread increases in correlation across the brain.
- Right TLE had focal change in correlation in parietal, occipital and frontal region groups.

Figure 1.
Spatial depiction of region group definitions based on 90 regions from the AAL atlas.
Further information on the regions and region groups used for analysis is provided in
Supplemental Table 1.

Figure 2.

Correlation group and difference matrices. A) The 90×90 groupwise volumetric correlation matrices (Fisher z) for individual groups (RTLE, LTLE, RCon and LCon). Each cell represents the Spearman rank correlation of two regional volumes across the group after linear detrending of total gray matter volume, age, and age². B) The z difference matrices (RTLE-RCon and LTLE-LCon) normalized using the standard deviation of the null distribution for each region pair. Regions are categorized by region group (full region list in Supplemental Table 1). L = left hemisphere regions and R = right hemisphere regions.

Figure 3.

RTLE-RCon estimated probability distribution of z differences grouped by A) Hemisphere, B) Temporal, C) Limbic, and D) Parietal region groups. Each plot contains the distribution of region pairs within the hemisphere or region group ipsilateral to the seizure focus (Ipsi), regions pairs contralateral to the seizure focus (Contra), and region pairs containing one in each hemisphere (Cross). RTLE = right temporal lobe epilepsy, RCon = controls age, gender and coil matched to RTLE. The negative x-axis values represent z differences where patients have decreased correlation, while the positive x-axis values indicate pairs where patients have increased correlation compared to controls. Increases on the y-axis indicate a region group with higher probability of increased or decreased correlation. The 2.5%, 50% and 97.5% percentile values are given for all analyses in Table 2.

Figure 4.

LTLE-LCon estimated probability distribution of z differences grouped by A) Hemisphere, B) Limbic, C) Temporal, and D) Subcortical region groups. Each plot contains the distribution of region pairs within the hemisphere or region group ipsilateral to the seizure focus (Ipsi), regions pairs contralateral to the seizure focus (Contra), and region pairs containing one in each hemisphere (Cross). LTLE = left temporal lobe epilepsy, LCon = controls age, gender and coil matched to LTLE. The negative x -axis values represent z differences where patients have decreased correlation, while the positive x -axis values indicate pairs where patients have increased correlation compared to controls. Increases on the y -axis indicate a region group with higher probability of increased or decreased correlation. The 2.5%, 50% and 97.5% percentile values are given for all analyses in Table 2.

Figure 5.

Graphical summary of volumetric correlation and difference findings. RTLE = right temporal lobe epilepsy. LTLE = left temporal lobe epilepsy. IPSI = ipsilateral to seizure foci. CONTRA = contralateral to seizure foci. Red shading indicates increased correlation in TLE compared to controls (see Table 2); Blue shading indicates decreased correlation in TLE compared to controls (see Table 2). * indicates region group where at least one region showed significant volumetric decrease compared to controls ($p < 0.01$). # indicates region group where at least one region showed significant volumetric increase compared to controls ($p < 0.01$).

Table 1

Patient characteristics

Patient Group	Age (years)	Gender	L/R Hipp Ratio	Age at Onset (years)	Epilepsy Duration (years)	CPS freq/month	Coil
RTLE (n=26)	40.5 ± 10.0	17 F, 9 M	1.12 ± 0.12 (conR: 1.02 ± 0.03)	19.7 ± 12.6	20.8 ± 13.6	13.3 ± 19.8	8(18)
LTLE (n=18)	34.5 ± 14.2	9 F, 9 M	0.95 ± 0.09 (conL: 1.02 ± 0.04)	11.7 ± 12.1	22.8 ± 16.3	9.9 ± 13.6	11(7)

Summary statistics (average ± standard deviation) for patient groups, RTLE and LTLE.
L/R Hipp Ratio = regional volume of left hippocampus divided by regional volume of right hippocampus using AAL atlas definition, ratio provides a measure of hippocampal asymmetry; CPS freq/month = number of complex partial seizures per month. Coil = number of subjects acquired with 8 channel (32 channel).

Table 2

Summary statistics for the normalized z difference distributions for RTLE and LTLE.

	RTLE				LTLE			
	2.5%ile	Median	97.5%ile	2.5%ile	Median	97.5%ile	2.5%ile	97.5%ile
Hemisphere	Ipsi	-1.75	0.04	1.77	-1.81	-0.02	1.93	
	Contra	-2.02**	0.05	2.03**	-1.83	0.25	2.15**	
	Cross	-1.92	-0.12	1.73	-1.95	-0.05	1.86	
Frontal	Ipsi	-1.82	0.00	1.83	-1.81	0.06	1.89	
	Contra	-2.13*	0.03	1.82	-1.84	0.26	2.11*	
	Cross	-1.92	-0.09	1.68	-1.98	0.04	1.96	
Limbic	Ipsi	-1.96	-0.10	1.58	-1.82	-0.02	1.76	
	Contra	-1.84	0.00	2.24*	-1.87	0.23	2.29*	
	Cross	-1.92	-0.18	1.76	-2.04*	-0.13	1.79	
Occipital	Ipsi	-1.69	0.03	1.80	-1.78	-0.10	1.77	
	Contra	-2.07*	0.14	1.86	-1.83	0.21	2.12*	
	Cross	-1.91	-0.03	1.72	-2.03*	-0.11	1.75	
Parietal	Ipsi	-1.52	0.27	1.87	-1.99	-0.05	2.00	
	Contra	-2.19*	0.02	1.68	-1.72	0.09	1.91	
	Cross	-1.97	-0.10	1.74	-1.77	0.07	1.80	
Subcortical	Ipsi	-1.68	-0.03	1.61	-1.98	-0.06	2.14*	
	Contra	-1.98	0.02	2.08*	-1.86	0.37	2.16*	
	Cross	-1.97	-0.10	1.74	-1.77	0.07	1.80	

	RTLE				LTLE			
	2.5%ile	Median	97.5%ile		2.5%ile	Median	97.5%ile	
Cross	-2.04 *	-0.16	1.81	-1.98	-0.07	1.92		
Ipsi	-1.86	0.07	1.83	-1.91	-0.16	1.92		
Contra	-2.15 *	0.20	2.29 *	-1.92	0.27	2.18 *		
Cross	-1.87	-0.16	1.71	-1.92	-0.20	1.73		

Values from z difference distributions (some shown in Figures 3 and 4) are summarized over region pairs within the hemisphere or region group ipsilateral to the seizure focus (Ipsi), regions pairs contralateral to the seizure focus (Contra), and region pairs containing one in each hemisphere (Cross). For the purposes of reporting the region groups most contributing to the hemispheric differences, we considered 2.5% percentile values less than -2.0 as decreased correlations compared to controls, while increased correlations were indicated by 97.5% percentile values greater than 2.0. RTLE = right temporal lobe epilepsy, LTLE = left temporal lobe epilepsy, RCon = controls age, gender and coil matched to RTLE, LCon = controls age, gender and coil matched to LTLE.

** denotes strongest hemispheric differences;

* denotes those values exceeding our threshold for indicating most contributing to hemispheric differences.