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Functional Connectivity Evidence of Cortico-Cortico Inhibition in Temporal Lobe Epilepsy

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Abstract

Epileptic seizures can initiate a neural circuit and lead to aberrant neural communication with brain areas outside the epileptogenic region. We focus on interictal activity in focal temporal lobe epilepsy and evaluate functional connectivity differences that emerge as function of bilateral versus strictly unilateral epileptiform activity. We assess the strength of functional connectivity at rest between the ictal and non-ictal temporal lobes, in addition to whole brain connectivity with the ictal temporal lobe. Results revealed strong connectivity between the temporal lobes for both patient groups, but this did not vary as a function of unilateral versus bilateral interictal status. Both the left and right unilateral temporal lobe groups showed significant anti-correlated activity in regions outside the epileptogenic temporal lobe, primarily involving the contralateral (non-ictal/non-pathologic) hemisphere, with precuneus involvement prominent. The bilateral groups did not show this contralateral anti-correlated activity. This anti-correlated connectivity may represent a form of protective and adaptive inhibition, helping to constrain epileptiform activity to the pathologic temporal lobe. The absence of this activity in the bilateral groups may be indicative of flawed inhibitory mechanisms, helping to explain their more widespread epileptiform activity. Our data suggest that the location and build up of epilepsy networks in the brain are not truly random, and are not limited to the formation of strictly epileptogenic networks. Functional networks may develop to take advantage of the regulatory function of structures such as the precuneus to instantiate an anti-correlated network, generating protective cortico-cortico inhibition for the purpose of limiting seizure spread or epileptogenesis.

Keywords

Epilepsy; Unilateral versus bilateral epileptiform activity; Connectivity; Resting-state; Cortical inhibition

Introduction

The abnormal, hypersynchronous neural activity initiated during an epileptic seizure may affect brain regions outside the ictal focus. Through both seizure spread, seizure generalization and the development of secondary epileptogenesis, the ictal focus of a seizure

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can be seen as initiating a neural circuit, a circuit that if instantiated repeatedly by ongoing seizures leads to frequent aberrant neural "communication" with other regions of the brain. Eventually, these epileptogenic pathways create a set of biased connections emerging from the ictal zone, a favored network that is both maladaptive to cognition and pathologic to otherwise healthy neural tissue as it now has to bear the burden of periodic epileptiform activity.

Resting state functional magnetic resonance imaging (rsfMRI) is a powerful neuroimaging tool that can be used to identify neural connectivity in the brain. In the setting of epilepsy, rsfMRI may be able to identify epileptic circuits, and, in so doing, provide clinicians and neurosurgeons with clues about where new epileptic foci may form, or where seizures are placing the most significant burden on the brain. Identifying such abnormal brain networks, particularly those that point to new or secondary epileptogenic foci, will be of great value to the selection of candidates for resective surgery as it is well known that patients with secondary epileptogenesis and bilateral epileptiform activity have a poorer outcome following surgery (Holmes et al., 1997). For instance, patients with strong signs of connectivity abnormalities, who are also showing EEG signs of multiple potential seizure foci would clearly be identified as poor candidates for resective surgery. Lastly, but importantly, from a neuroscience perspective, demonstrating different patterns of abnormal connectivity in different types of epilepsy patients will have implications for our understanding of maladaptive, and perhaps even adaptive, neural circuit formation and development.

While it is readily known that generalized clonic-tonic seizures (Wang et al., 2010) and absence seizures (Luo et al., 2011) can disrupt neural connectivity patterns and cause dysfunction outside the region of ictal activity, there is also evidence that such remote effects emerge from focal temporal lobe epilepsy (TLE) (Liao et al., 2010; Waites et al., 2006). For instance, MRI measurements of cortical thickness appear to decline over time in both the ictal temporal and contralateral temporal lobe (Bernhardt et al., 2009). A finding with similar implications comes from Bonilha and colleagues (Bonilha et al., 2007; Riederer et al., 2008) who used voxel-based morphometry (VBM) to demonstrate that hippocampal atrophy in the epileptogenic temporal lobe is associated with extrahippocampal atrophy involving the contralateral hippocampus and parahippocampal gyri. A study by Riederer and colleagues used VBM to demonstrate neural network damage outside the mesial temporal lobe in TLE patients, with the additional observation that such extratemporal damage is more widespread in left compared to right-sided TLE (Riederer et al., 2008). Thivard and colleagues (2005) used diffusion tensor imaging to show that TLE patients compared to normal healthy controls had decreased diffusivity in the contralateral non-sclerotic hippocampus, amygdala, and temporal pole. Arfanakis et al. (2002) showed that diffusivity abnormalities in TLE patients was not restricted to the known epileptogenic temporal lobe, but extended to other brain regions such as the posterior corpus callosum. Finally, evidence of metabolic compromise from Magnetic Resonance Spectroscopy derived NAA/choline ratios in extratemporal regions, including the contralateral hemisphere, suggests that seizures in TLE can exert remote deleterious effects on neural integrity, and such effects are not be visible on MRI (Cendes et al., 1997; Tasch et al., 1999; Vermathen et al., 2003).

Studies of functional connectivity also appear to suggest connectivity changes occur in focal epilepsy patients in areas outside the epileptogenic temporal lobe. Liao and colleagues (2010) demonstrated altered connectivity in TLE patients, involving increased connections within the mesial temporal lobe, and decreased connectivity to extratemporal areas. Seidenberg et al. (2005) reported broad connectivity disturbances in temporal lobe epilepsy patients including contralateral temporal regions when compared to normal controls (Bettus et al., 2009; Seidenberg et al., 2005). Other studies have suggested there is a propensity

towards bilateral connectivity changes in patients with unilateral epilepsy patients (Morgan et al., 2011; Pereira et al., 2010). All the above is consistent with the possibility that the diseased epileptogenic temporal lobe is having a deleterious impact on the whole brain, potentially impacting multiple cerebral networks.

Importantly, none of the above studies distinguished between extratemporal disruptions in patients with focal epilepsy where there is no evidence of epileptiform activity outside the temporal lobe, and epilepsy patients, where in addition to an ictal focus, there is evidence of distinct epileptiform disturbances outside the temporal lobe. This distinction is subtle but crucial as it is this latter group of patients who should show patterns of functional network change potentially indicative of abnormal, maladaptive neural network formation. Thus, it is this group that can potentially allow us to view the properties and characteristics of developing epileptogenic networks, perhaps even those moving towards the formation of independent foci.

How common is such widespread bilateral epileptiform activity in the context of focal temporal lobe epilepsy? The literature comparing unilateral and bilateral interictal epileptic discharges suggests that the incidence of bilateral interictal epileptiform discharges in TLE varies from 8–42% (Ergene et al., 2000). With the yearly prevalence of TLE patients estimated at 780,000 (Manford et al., 1992; Sander, 2003), the number of TLE patients with potential widespread connectivity abnormalities is substantial.

In this study, we focus on extratemporal interictal activity in focal TLE and assess for connectivity changes that emerge as function of the bilateral seizure activity. To accomplish this we assess functional connectivity in two types of focal TLE patients, one with strong evidence of restricted focal seizure effects, and the other with strong signs of bilateral epileptiform activity indexed by EEG evidence of interictal (not ictal) activity in the non-pathologic, contralateral temporal lobe. We hypothesize that focal TLE patients with bilateral activity will show evidence of extensive functional connectivity (FC) emerging from the epileptogenic (ictal) temporal lobe. More specifically, we expect patients with such bilateral activity to show strong connectivity to the contralateral (non-ictal) temporal lobe, as that is the locus of the inter-ictal activity outside the epileptogenic temporal lobe. Focal TLE patients without such EEG evidence, whose epileptiform activity is restricted to the pathologic, epileptogenic (ictal) temporal lobe, are not expected to show the above pattern of bilateral connectivity.

In the development of disturbances outside the epileptogenic temporal lobe, the chronicity of seizures is likely a key factor. A longer duration of illness, for instance, gives more time for the neuroplasticity responses associated with epileptiform activity (e.g., mossy fiber sprouting, GABA and calcium channel alterations) to develop. Hence, we also examine the role of chronicity as indexed by years since diagnosis of the epilepsy (duration of illness).

Material and Methods

Participants

A total of 25 left temporal lobe epilepsy and 23 right temporal lobe epilepsy patients were recruited from the Thomas Jefferson Comprehensive Epilepsy Center. The two TLE groups consisted of patients who were recommended for unilateral anterior temporal lobe resections (ATL, left or right) as treatment for their intractable temporal lobe epilepsy. Nevertheless, all the patients did not go on to have surgery (54% had an ATL resection (n=26)). All participants were scanned prior to surgery. Details of the Thomas Jefferson Comprehensive Epilepsy Center algorithm for surgical decision making are described elsewhere (Sperling et al., 1992). The clinical characteristics of the sample are described in Table 1.

A complete history was taken, and a combination of EEG, MRI, PET, Intracarotid Amobarbital Procedure (IAP), and neuropsychological testing was used to lateralize the side of seizure focus. All patient participants met the following inclusion criteria: unilateral temporal lobe seizure onset through surface video/EEG recordings (i.e., a single unilateral temporal lobe focus); MRI or PET evidence of temporal lobe pathology confirming the presence of temporal lobe atrophy, most commonly mesial temporal sclerosis, in the epileptogenic temporal lobe; concordant PET finding of hypometabolism in the temporal lobe (available for most patients); Full-Scale IQ (FSIQ) of at least 75. TLE participants were excluded from the study on grounds of any of the following: medical illness with central nervous system impact other than epilepsy; head trauma; prior or current alcohol or illicit drug abuse; extratemporal or multifocal epilepsy (a likely ictal focus outside the one temporal lobe); contraindications for MRI; psychiatric diagnosis other than a Depressive Disorder or hospitalization for an Axis I disorder listed in the Diagnostic and Statistical Manual of Mental Disorders, IV. Depressive Disorders were allowed given the high co-morbidity of depression and epilepsy (Tracy et al., 2007). Participants provided written informed consent. The study was approved by the Institutional Review Board for Research with Human Subjects at Thomas Jefferson University. Table 1 outlines the demographic and clinical characteristics of the participants.

EEG Procedures

EEG was obtained using the 10–20 system with anterior temporal electrodes and, at times, sphenoidal electrodes that used a Grass-Telefactor 32 channel acquisition system. At least 96 hours of continuous EEG recording was utilized. Selected samples in wakefulness and sleep were examined by registered EEG technologists, board certified electroencephalographers (MS, CS), and a commercial automated spike detection program (SZAC, Grass Telefactor) to determine the location and lateralization of interictal spikes and seizures.

Patient Classification

The main criterion for inclusion in the study was that all patients have unilateral pathology and a unilateral ictal focus. Patients who met these criteria, but who also showed signs of interictal activity in the contralateral temporal lobe (i.e., possible early signs of developing a contralateral seizure focus) were chosen for the Bilateral Groups. More specifically, patients with unilateral ictal and interictal temporal lobe spikes ipsilateral to the epileptogenic (pathologic) zone maximal in anterior temporal, midtemporal or basal temporal electrodes with no epileptiform activity elsewhere, were defined as the *Unilateral Focus* Groups, involving the left (n=14) or right (n=13) temporal lobe accordingly. Patients with interictal spikes in both the ipsilateral (ictal, temporal lobe pathology) and contralateral temporal lobes (spike maximum in anterior temporal, midtemporal or basal temporal electrodes) were defined as the *Bilateral Focus* Groups (left, n=11; right, n=10); see Figure 1. Patients with bilateral epileptogenic (ictal) activity were excluded from the bilateral group, as bilateral independent foci likely represent separate pathophysiologic processes, or an advanced stage of pathologic recruitment. In the Bilateral groups, the contralateral interictal activity was not associated with an ictus or abnormal MRI. Thus, our grouping method captures unilateral seizure focus patients who show unilateral versus bilateral interictal spiking. Note, patients within each of our groups who generalized and/or secondarily generalized seizures were identified. Among the patients identified with secondary generalized seizures, in no individual case was this the primary seizure type (complex partial was always the primary type for these patients), and in no case did the number of these secondarily generalized seizures exceed 10 (lifetime). Among the patients identified with generalized seizures (either tonic-clonic or absence), in no case was this the primary seizure type (complex partial was

the primary seizure for all these patients), and in no case did the number of these generalized seizures exceed, also, 10 (lifetime).

rsfMRI Scanning Parameters

All patients underwent Magnetic Resonance Imaging on a 3-T X-series Philips Achieva clinical MRI scanner (Amsterdam, the Netherlands) using an 8-channel head coil during a two-year period (12/2008–12/2010). There were no changes to the scanner software (reconstructer version 8), hardware, or sequence during that time. Participant data were collected in a pseudo-randomized, interleaved fashion (i.e. no single patient group was scanned at a different time than other groups), so as to not introduce any bias based on temporally dependent scanner calibration.

Single shot echoplanar gradient echo imaging sequence acquiring T2* signal was used with the following parameters: 34 axial slices acquired parallel to the AC-PC line, TE=35ms, TR=2.5 seconds (interleaved, contiguous collections), FOV=256 mm, 128×128 data matrix isotropic voxels, flip angle=90°, bandwidth=1.802(±241.1 kHz), slice thickness= 4mm. The in-plane resolution was 2*2 mm^2. Prior to collection of the T2* images, T1-weighted images (180 slices) were collected using an MPRage sequence (256×256 isotropic voxels; TR=640 ms, TE=3.2 ms, FOV 256 mm, flip angle 8°) in positions identical to the functional scans to provide an anatomical reference. The resolution for each T1 slice was 1 mm^3 (axial oblique; angle following anterior, posterior commissure line). Survey and field reference inhomogeneity images were collected prior to the start of the study. Each EPI imaging series started with three discarded scans to allow for T1 signal stabilization. Subjects lay in a foam pad to comfortably stabilize the head, were instructed to remain still throughout the scan, not focus on any particular activity or thing, and keep their eyes closed during the entirety of the scan. Any scan where motion artifact significantly impacted image quality was discarded and repeated. The rsfMRI scan took five minutes to complete.

Imaging Processing and Statistical Analysis

SPM8 (http://www.fil.ion.ucl.ac.uk/spm/software/spm8) and the Functional Connectivity Toolbox v1.2 (http://www.nitrc.org/projects/conn) were utilized for the pre-processing and statistical analysis of all images. Slice timing correction was used to adjust for variable acquisition time over slices in a volume, with the middle slice in every volume used as reference. A six parameter variance cost function rigid body affine registration was used to realign all images within a session to the mean volume. Motion regressors were computed and later used as a regressor of no interest in the first level, subject specific analysis. To maximize mutual information, coregistration between functional scans and the MNI305 template was carried out using six iterations and resampled with a 7th-Degree B-Spline interpolation. Functional images were then normalized and wrapped into standard space (MNI305) to allow for signal averaging across subjects. We utilized the standard normalization method in SPM8, which minimizes the sum-of-squared differences between the subject's image and the template (MNI305), while maximizing the prior probability of the transformation. This spatial normalization begins by determining the optimum twelve-parameter affine transformation to account for differences in position, orientation and overall brain size. After affine transformation, a nonlinear transformation is applied to correct for gross differences in head shape that were not accounted for by the affine transformation. The nonlinear deformations are described by the lowest frequency components of three-dimensional discrete cosine transform basis functions (Ashburner & Friston, 1999). The three major parameter estimation settings involving nonlinear frequency cutoff, nonlinear regularization and the number of nonlinear iterations, were all set to the SPM defaults, namely: 25 mm, medium regularization, and 16 nonlinear iterations, respectively.

Tissue probability templates and the segmentation algorithm of SPM were utilized to segment images into white matter, gray matter, and cerebrospinal fluid. Segmentation parameter settings included a very light bias regularization (.0001) and a full width half maximum kernel of 60mm to correct for spatially varying artifact that may modulate the intensity of the image. The Compcor procedure was also utilized for reducing physiological and other noise (Behzadi et al., 2007). In this procedure, significant principal components are drawn from regions not likely modulated by neural activity. The components are then represented in the design matrix and their variance is partitioned from the variables of interest. Next, a band-pass temporal filter was applied to remove high and low frequency fluctuations (.008 to .09 Hz) (Cordes et al., 2001). Lastly, all images were smoothed by convolution with a Gaussian kernel, with a full width at half maximum of 8 mm in all directions to increase the signal to noise ratio and to meet the assumptions of the statistical tests (e.g., normality).

Regions of interest (ROIs) covering the epileptogenic zone in the right and left temporal lobe were constructed and utilized in the analyses. These ROIs essentially captured the regions of cortex, including white matter, that would be resected in our typical anterior temporal lobe (en bloc) resection. The rationale for this ROI was to be sure to capture the full extent of the areas potentially generating epileptiform activity, including the epileptogenic (ictal onset) and the irritative zones of the seizures, beyond just the sclerotic or atrophic area, as a means of increasing the likelihood of seizure control. At our center this standard anterior temporal lobectomy resects approximately 4 cm back from the temporal pole, including 3 **cm** of lateral cortex (4 cm in the case of non-dominant resections), and 2–3cm of the hippocampus depending on the vascular anatomy. The ROI mask was drawn on the MNI 305 anatomical template. The mean value for the ROI at each collected time point (120 volumes) was then calculated, yielding separate (averaged) time series data for left and right temporal lobe ROIs.

Group-level analyses first involved estimation of the strength of FC between average times series of the two temporal lobe ROIs, run separately within each of the four experimental groups. A bivariate correlational procedure was used estimating the FC between the left and right Temporal lobe ROIs in each experimental group. The procedure yielded standardized beta values for each group. A two-way Analysis of Variance (ANOVA) on the beta values was then conducted with two between-subject factors Laterality (Unilateral versus Bilateral epileptiform activity) and Side of Ictal Focus (Left versus Right Temporal Lobe). Both main effects and the interaction were included in the model. This ANOVA allowed us to determine, for instance, whether the strength of resting state connectivity differed in the Bilateral and Unilateral Groups, and, if so, whether this was a function of Side of Ictal Focus.

Next, whole brain FC with the ictal temporal lobe was determined with the left temporal lobe ROI used as a seed for the left-sided groups (Left Unilateral, Left Bilateral) and the right temporal lobe ROI used as a seed for the right-sided groups (Right Unilateral, Right Bilateral). Again, correlational procedures were used to estimate the relevant whole brain functional connectivity emerging from the seed, with each of the four experimental groups assessed separately (e.g., the left temporal lobe ROI as seed for the Left Unilateral Group). Results for the above analyses utilized a height threshold of at least $p \leq 0.05$ (Family Wise Error, FWE), and a spatial extent threshold of at least $p<.05$ (false discovery rate, FDR).

As bilateral epileptiform activity has been associated with longer duration of epilepsy (Ergene et al., 2000), we investigated the effects of seizure chronicity. To accomplish this epilepsy duration (in years) was examined in association with each of the individual groups for those contrasts where we found significant effects (i.e., Unilateral Left and Unilateral

Right Group). This allowed us to identify those voxels that were specifically sensitive to both the covariate and Group membership. As an additional check, the significant effects involving the individual Unilateral Groups were rerun for the relevant effects (e.g., Left Unilateral whole brain connectivity with Left Temporal Lobe ROI seed) with a covariate of no interest represented in the model (epilepsy duration). This allowed us to verify that the variance associated with the relevant effects remained significant after accounting for the variance unique to the duration covariate. In all cases, the original effect remained significant after accounting for this duration covariate. Results for the above analyses utilized a height threshold of at least $p \leq 0.05$ (FWE), and a spatial extent threshold of at least $p<.05$ (FDR).

Results

Table 1 displays the clinical and demographic data for the Unilateral and Bilateral Groups. The groups did not differ on any of the variables listed as tested by t-test (age, education, duration of epilepsy, Full Scale IQ, and handedness) or chi square statistics (gender).

In all four TLE groups, the beta values measuring the association between the two ROIs were nearly threefold greater than the beta values estimating the degree of non-specific connectivity to all gray matter emerging from either of the two ROIs (n.b. gray matter serves as a valuable point of comparison to examine the strength of the selective connectivity of each ROI). The FC between the two temporal lobe ROIs was strong, however, and this connectivity did not vary by Experimental Group as the ANOVA involving Laterality (Bilateral and Unilateral Groups) and Side (Left and Right Groups) produced null main effects and no significant interaction ($p<.05$ was used). As can be seen in Table 2, the FC beta values for each of the experimental groups are quite similar.

Table 3 displays whole brain resting state connectivity data for each group using the left temporal lobe ROI as seed for the Left Unilateral and Bilateral Groups and the right temporal lobe ROI as seed for the Right Unilateral and Bilateral Groups (see Table 3). The left Unilateral Group using the left ROI as seed displayed positive connectivity outside the ROI seed in an ipsilateral area of inferior frontal cortex (BA 44) and a posterior temporal region (BA 21/37). The left Unilateral Group, with this same seed, showed a negative connectivity to two right hemisphere regions including the precuneus (BA 18, bilateral but more right) and right middle frontal gyrus (BA 10) (see Table 3 and Figure 2a and 2b).

The Right Unilateral Group using the right ROI as seed was found to have positive connectivity with a fairly broad area outside the ROI involving right frontoparietal cortex and opercula. The right unilateral group, showed negative connectivity with the left hemisphere involving the left superior parietal lobule (BA 7), bilateral cuneus and precuneus (BA 18), left middle frontal gyrus (BA 10), left inferior frontal gyrus (BA 47), bilateral medial frontal gyrus (BA 8) (see Table 3 and Figures 3a and 3b).

The Left Bilateral group was found to no have positive connectivity to regions outside the left ROI, and no connectivity, negative or positive, between the left temporal ROI and any right hemisphere regions (see Table 3). The Right Bilateral group was found to show some positive connectivity between the right ROI and the right frontal opercular (BA 6), in addition to a region in the left hemisphere (superior parietal cortex, BA 7).

A contrast comparing the Left Unilateral and Bilateral Groups revealed no reliable differences. However, when a lower height threshold was used (FWE, $p<.08$) the left Unilateral Group demonstrated greater negative connectivity in the right hemisphere in regions very similar to those shown in Figure 2b. Note, this comparison between the Unilateral and Bilateral groups only speaks to a relative difference in negative connectivity

in the right hemisphere; the analysis of the Left Bilateral Group alone shows it does not have statistically significant connectivity with the right hemisphere. Comparable results were found comparing the Right Unilateral and Bilateral Groups, indicating no statistically reliable differences were present, though again a lower height threshold (FWE, $p<.07$) revealed greater negative connectivity in the left hemisphere for the Right Unilateral Group.

Whole brain FC analyses examining the main effect for the Left Laterality Groups (Unilateral and Bilateral combined), utilizing the left temporal lobe ROI as seed, revealed significant positive connectivity only with the right temporal lobe ROI region (beta=.44, $t=7.93$, $p<.0001$). A comparable finding was observed for the main effect of the Right Laterality Groups (Unilateral and Bilateral combined) with the right temporal lobe ROI used as seed. Here, significant positive connectivity was observed only with the left temporal lobe ROI region (beta=.53, $t=9.25$, $p<.0001$).

As noted, duration of the epilepsy illness may be a strong mediating factor in the emergence of secondary epileptogenesis. Hence, we examined whether the connectivity in our experimental groups was associated with duration of epilepsy (in years). Within the Left Unilateral Group the FC associated with long duration eplilepsy emerging from the left temporal lobe ROI showed an area of positive connectivity with a posterior temporal region (BA 21/37), and an area of negative connectivity with a right occipital/precuneus region (BA 18; see Table 4, Figure 4a). The Left Bilateral Group with the left temporal lobe as seed showed positive connectivity outside the ROI with a set of left hemisphere regions (inferior temporal, BA 20, beta=.34; inferior frontal gyrus, BA 11), in addition to a negative association with the bilateral thalamus.

Within the Right Unilateral Group the connectivity associated with long duration epilepsy emerging from the right temporal lobe ROI showed an area of positive connectivity involving an inferior frontal region outside the seed (BA 44), and an area of negative association between the ROI and a midline/bilateral occipital/precuneus region (BA 18; see Table 4, Figure 4b). The Right Bilateral group, with the right temporal lobe as source, showed no significant effect with epilepsy duration.

Discussion

In our TLE sample, the correlation between the two temporal lobes appeared to be positive and did not vary by experimental group, suggesting that this connectivity is not altered by the presence of interictal activity in the contralateral temporal lobe. In the case of the Bilateral Groups, our data suggest that in the absence of detectable structural damage in regions contralateral to the primary epileptogenic focus, these areas with epileptiform (interictal) activity do show strong functional connectivity to the ictal temporal lobe. In the case of the Unilateral Groups, TLE patients showed significant anti-correlated activity in regions outside the ictal temporal lobe, most strongly involving the contralateral (non-ictal) hemisphere, with the precuneus a prominent location for the negative connectivity in both groups. In contrast, neither of the Bilateral groups shows such contralateral (non-ictal) anti-correlated activity, a quite striking finding.

When functional connectivity patterns associated with longer duration of seizures are taken into account in the Unilateral Groups, the negative connectivity with areas outside the temporal lobe was more spatially limited than in the original Unilateral Group analyses, involving only the precuneus (see Table 4 and Figure 4). Thus, in the case of both the Left and Right Unilateral Groups individuals with longer duration of epilepsy showed strong negative connectivity between the ictal temporal lobe and the precuneus region. No significant effect associated with duration was observed in the Right Bilateral Group. For

the Left Bilateral Group, a set of left hemisphere regions (inferior temporal, right frontal) showed increased positive connectivity with the Left Temporal ROI in association with longer duration epilepsy, and one region, the ventral thalamus, showed negative connectivity.

The positive correlation between the two temporal lobes indicates that their BOLD signals are synchronized and run in the same direction, an effect present in all the experimental groups. **Nevertheless,** the strength of the association between the temporal lobes is slightly higher in each Bilateral Group (see Table 2) compared to its Unilateral counterpart, a feature that would be considered consistent with epileptogenesis in the temporal lobe contralateral to the ictal focus, but the groups did not statistically differ in this regard. In light of evidence showing that positive functional connectivity between temporal lobe regions (particularly the superior temporal lobes) is present in normals (Doucet et al., 2011), **we suggest** that the strong temporal lobe connectivity we have observed **may** represent a normal variant **(for more information, see the limitation section)**.

For the Unilateral groups the presence of anti-correlated activity on the contralateral side indicates that the BOLD signal runs in the opposite direction of the temporal lobe ROI seed. It is important to note that the anti-correlations involving the non-ictal hemisphere only indicate synchronized and associated neural activity (Fox et al., 2009). They do not indicate which regions involved in the association demonstrate negative activity (absent or lower activation levels) and which regions are showing positive activity (higher activation levels). The true significance of negative correlations remains a matter of debate. Some argue that it may be the result of preprocessing (Murphy et al., 2009). Yet, this would not explain the difference we are observing between the Unilateral and Bilateral groups, as each received identical preprocessing. We suggest the anti-correlations we observed are not artifactual and do have biological meaning. One viable interpretation of the anti-correlations is that the opposite level of activity in the contralateral, non-ictal hemisphere represents protective, adaptive inhibition, perhaps helping to constrain and limit ictal activity to the pathologic temporal lobe. The absence of this counterpoised relationship in the Bilateral groups may be indicative of flawed inhibitory mechanisms, and this flaw is consistent with the known property of these Groups, i.e., bilateral epileptiform activity. Epileptiform neurophysiological activity is known to lead to not just excitatory, but also local (Tebartz van Elst et al., 2011) and remote inhibitory activity (De Tiege et al., 2008) in connected brain regions. Such inhibitory neurotransmission has been demonstrated in epilepsy through postmortem and tissue studies, and appears to be governed by increased expression of the extrasynaptic $GABA_AR\alpha5$ subunit which mediates tonic GABAergic inhibition in CA 1 pyramidal and dentate gyrus cells ((Hines et al., 2011); for evidence with rat models see (Ge et al., 2011)). Thus, the Bilateral Groups contralateral interictal activity may be compromising that hemisphere's inhibitory capacity. The data with duration showed that the precuneus, which appeared to be a prominent area for this anti-correlated activity, was strongly associated with long duration epilepsy. Chronicity seems to result in stronger connectivity between the epileptogenic temporal lobes and the precuneus, perhaps suggesting this is a connection that strengthens over the course of seizure activity, helping to create the system of cortico-cortico inhibition we observed for the Unilateral Groups. The absence of anti-correlated activity in the Bilateral groups may suggest these patients lack this protective, inhibitory cortico-cortico activity, and, as a result, interictal activity has successfully developed in the non-ictal, contralateral hemisphere. Our data suggest that it is contralateral interictal activity that degrades the protective neural force of inhibitory activity. Of course, our data do not prove such cortico-cortico inhibitory activity is present, but is consistent with it. It may require postmortem tissue analysis of GABAergic receptor and cell properties to provide a more definitive test of the concept.

Our data are consistent with other reports showing broad connectivity disturbances in temporal lobe epilepsy patients (Bettus et al., 2009; Seidenberg et al., 2005). Such studies have suggested there is a propensity for the build-up of positive, bilateral connectivity changes in unilateral epilepsy patients (Araújo et al., 2006; Babb, 1991; Quigg et al., 1997). A study by Koutroumanidis et al. (2000) did suggest there is a degradation of inhibitory mechanisms in temporal lobe epilepsy with bilateral epileptiform activity, but this study did not determine whether the connectivity pattern was a function of unilateral versus bilateral epileptiform states. Thus, a most important difference with our study is that these studies did not distinguish and test for differences between focal TLE patients with and without Bilateral epileptiform activity. This distinction allowed us to see that, indeed, bilateral positive connectivity is present between the temporal lobes in both left and right TLE, but that anti-correlated activity is also present elsewhere in the brain in the unilateral patients, potentially serving a distinct protective function in that group.

The precuneus is known to be an important structure (a “hub”) of the default network, a system that is active when the brain is at rest and down regulates when the brain is engaged in focused, controlled cognitive activity (Fransson & Marrelec, 2008; Shulman et al., 1997). Taking our data into account, one may propose that the precuneus is a regulating structure helping to set in place counterpoised activity not just in relation to cognitive activity, but also in relation to seizure activity. This role in epilepsy is consistent with its role as a hub in a major neural network in the brain (i.e., the default mode), a network whose key functionality may be helping to maintain in the brain a baseline state of equilibrium or readiness.

Our study is the first direct comparison of functional connectivity differences between focal TLE patients with solely unilateral versus bilateral interictal activity, the first to show that the presence of protective anti-correlated activity in the contralateral hemisphere may be a distinguishing feature of the Unilateral group, and the first to show that the failure of such may an important feature of the Bilateral group, helping to explain that group's more widespread epileptiform activity. As a caveat, we should note that a number of patients in all our groups, particularly the Left Bilateral group, had some secondarily generalized or generalized seizures, though in no case were these the primary seizure type, and in no case did these exceed ten in number. While our grouping scheme emphasizes the presence of contralateral interictal activity, we should note that this other generalized activity may have played a role in our finding involving contralateral anti-correlated activity. Also, we must acknowledge that while the majority of our patient sample had mesial temporal sclerosis, other pathologies were present. There was no indication of pathology outside the unilateral (ictal) temporal lobe in any of the patients by any neurodiagnostic measure other than the EEG data used to define our groups. Nevertheless, we cannot exclude the possibility that these pathologies have influenced our findings in unforeseen ways.

We should also note that though our clinical groups are relatively small, the beta values in all four groups measuring the association between the two temporal lobe ROIs were nearly threefold greater than the beta values estimating the degree of non-specific connectivity to all gray matter emerging from either of the two ROIs. This suggests that the statistical effects we are reporting are not just statistically significant, but also are selective, specific, and substantive in terms of the magnitude of connectivity.

In terms of epilepsy treatment, our finding of correlated neural signaling has implications for diagnostic methods. Resting state fMRI can help determine if regions in the contralateral hemisphere are signaling the ictal zone with anti-correlated activity. It may be that loss of this signaling, in the context of bilateral interictal EEG activity, is a poor prognostic sign as it indicates the loss of beneficial inhibitory activity. In contrast, the presence of this

signaling in the absence of bilateral interictal EEG activity may be a good prognostic sign as it indicates that the unilateral epileptiform activity is quite focal, is not burdening other regions, has not spread, and is protected and limited by strong inhibitory activity. In this way, techniques such as resting state MRI may help with the accurate selection of candidates for focal epilepsy surgery, aid in the planning of potential staged surgeries, and influence informed consent regarding potential surgical outcome.

Limitations

A major limitation of this study is likely the lack of healthy controls. The present results highlight statistical differences in resting state functional connectivity between the Bilateral versus Unilateral temporal lobe groups. Such results remain valid without a control group, and to the best of our knowledge, no previous study has described such results in TLE. We acknowledge, however, that with the present data we cannot discern whether the positive connectivity observed between the temporal lobes represents a normal variant (i.e., signaling over a normal pathway), secondary epileptogenesis (Morrell, 1985), or indicates that focal temporal lobe epilepsy is a bilateral disease even though a unilateral ictal focus is present (Blume et al., 1993; Cascino et al., 1996; Steinhoff et al., 1995; Williamson et al., 1993). Also, regarding the role of the precuneus as a regulating structure in epilepsy, a fuller test of this idea would also require inclusion of a normal control group, but our basic finding regarding anti-correlated differences between our groups is valid without such.

Another limitation may be that approximately half (26 of 48) the patients underwent surgery. Information on seizure outcome, with evidence of good seizure control, would have provided more assurance that the ROI (the resected region) we chose contained the epileptogenic zone. The ROI we constructed, matching the standard en bloc resection at our center, was the best way with reasonable confidence, short of implant recordings, to be sure to capture the seizure generator in a systematic manner that could be applied across patients. We reiterate that there was no evidence of pathology outside the temporal lobe in these patients, all patients had focal seizures as the primary type, and none had more than a handful on non-focal seizures (lifetime), which in the majority of cases was related to medication lapses. Even with highly focal lesional cases, there is always concern that the epileptogenic zone is broader than the lesion, thus the presumptive epileptogenic region, and the extent of resection almost always extends beyond the focal region of the probable ictus. Based on the 26 patients that had surgery, only one showed no seizure reduction in the first year, suggesting that the ROI we utilized likely included the seizure generator for our patients. Within the limits of the current technology for standard clinical cases, short of implantation and following the patients for years to obtain Engel outcome data, we believe we can assert with a reasonable level of confidence that the epileptogenic zone is within the ROI we have chosen though clearly not in identical regions within that zone for all patients. Unfortunately, the sample size of patients with post-surgery information was too small and too different amongst the four experimental groups to conduct statistical analyses based on seizure outcome. We acknowledge that, ultimately, our data remain silent on the exact location of the ictal focus.

Finally, we emphasize epileptiform activity as the underlying force behind the anti-correlated effect we observed, as such epileptiform activity was the key and active difference between our experimental groups. We realize that this does not preclude a role for the underlying pathology, or for the structural integrity of extratemporal regions, in such reorganization processes. Ultimately, our data do not allow us to distinguish between these possibilities.

Conclusion

In short, to the degree that there is functional (e.g., resting state fMRI) evidence consistent with anti-correlated activity in contralateral (non-ictal) brain regions in the absence of interictal epileptiform activity elsewhere in the brain, the risk for poor seizure control after surgery decreases. Lastly, it is important to note that our data suggest that the location and build up of epilepsy networks in the brain are not truly random, and are not limited to the formation of strictly epileptogenic networks. Functional networks may develop to take advantage of the regulatory function of structures such as the precuneus to instantiate an anti-correlated network in order to generate protective cortico-cortico inhibitory activity to limit seizure spread or epileptogenesis.

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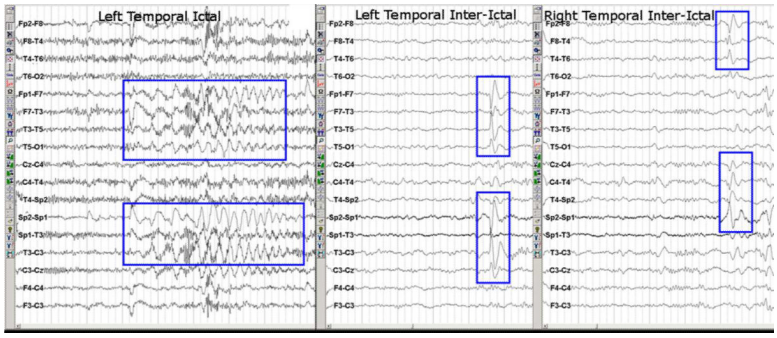

Fig. 1a.

EEG readings from a left bilateral patient with left temporal ictal and interictal activity with right temporal interictal activity.

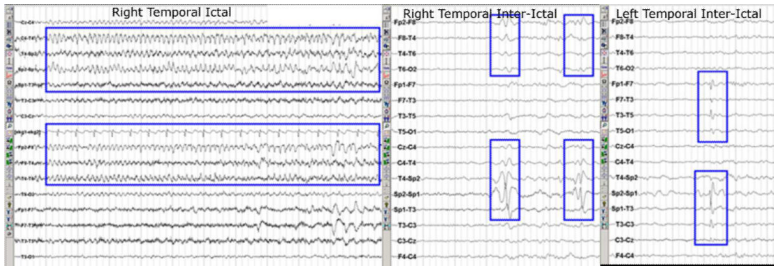

Fig. 1b.
EEG recordings from a right bilateral patient with right temporal ictal and interictal activity with left interictal activity.

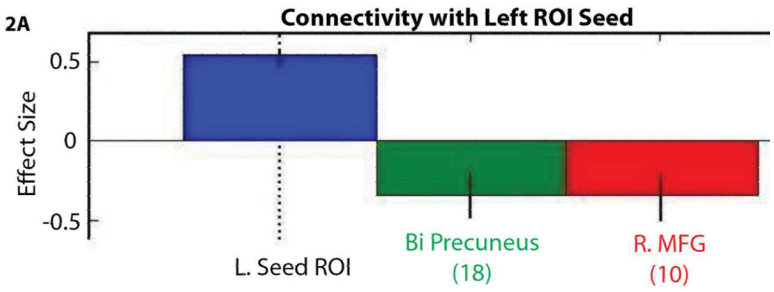

Fig. 2a.

Histogram of connectivity effect sizes and connectivity coefficients (betas) with left temporal lobe ROI in Left Unilateral group.

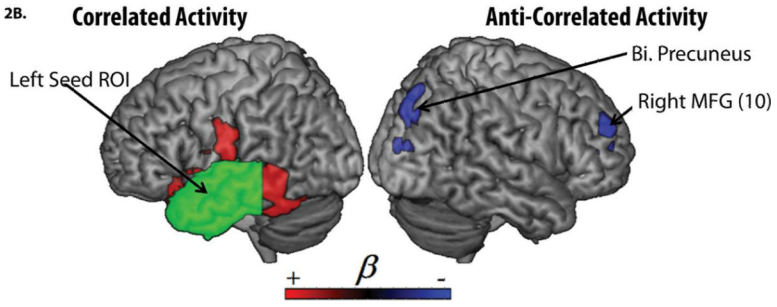

Fig. 2b.

Positive (red) and negative (blue) functional connectivity with the left temporal lobe ROI (green) in Left Unilateral patients. Data are in Table 3.

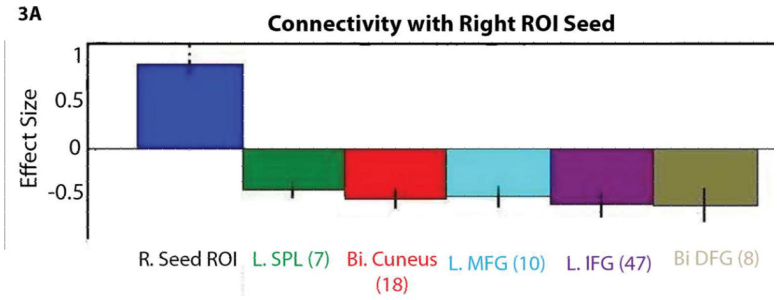

Fig. 3a.

Histogram of connectivity effect sizes and connectivity coefficients (betas) with right temporal lobe ROI in Right Unilateral group.

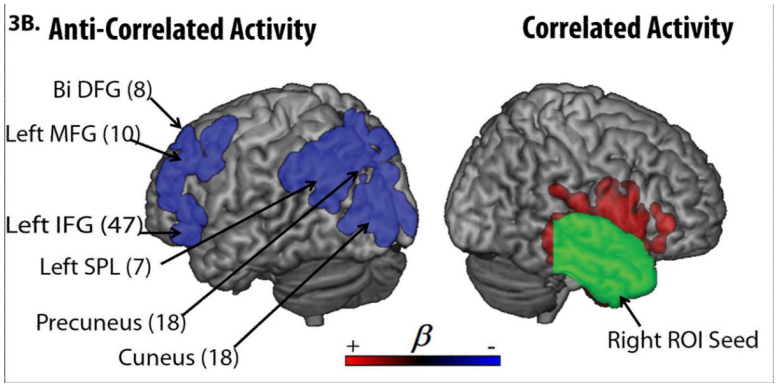

Fig. 3b.

Positive (red) and negative (blue) functional connectivity with the right temporal lobe ROI (green in Right Unilateral patients. Data are in Table 3.

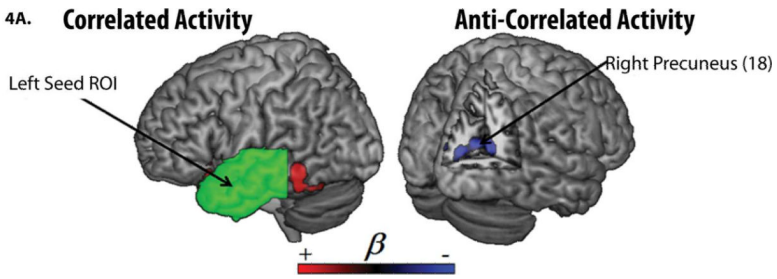

Fig. 4a.
Functional connectivity associated with high duration of epilepsy in Left Unilateral Group.

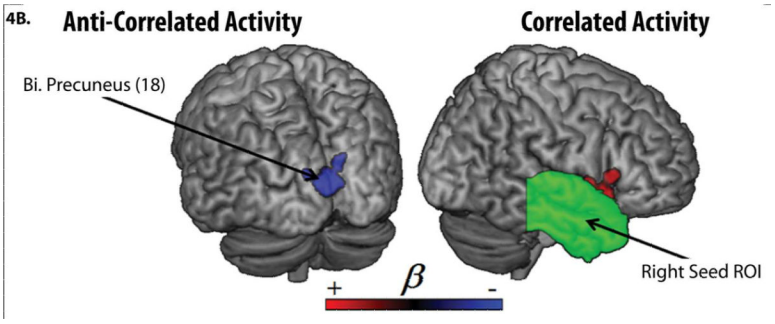

Fig. 4b.

Functional connectivity associated with high duration of epilepsy in Right Unilateral Group. Positive connectivity is in red, anti-correlated activity in blue, and the seed is in green. Data are in Table 4.

Table 1

Clinical and Demographical information for the Unilateral and Bilateral Groups.

Variables	Left Unilateral (n=14)	Right Unilateral (n=13)	Left Bilateral (n=11)	Right Bilateral (n=10)
# of males/females	10/4	8/5	9/2	7/3
	Mean ± STD	Mean± STD	Mean± STD	Mean± STD
Age at Scan (yrs.)	37.9 ± 11.9	40.0 ± 16.6	46.7 ± 7.4	39.8 ± 12.7
Years of Education	13.9 ± 2.1	14.4 ± 2.2	14.7 ± 2.6	14.0 ± 2.4
Edinburgh Handedness score	75.3 ± 53.3	77.8 ± 46.7	76.4 ± 59.4	70.0 ± 61.1
Duration of Epilepsy (yrs.)	15.6 ± 12.9	20.2 ± 14.1	23.5 ± 17.8	10.6 ± 9.1
Full Scale IQ	95.5 ± 12.2	99.6 ± 11.9	93.7 ± 13.3	95 ± 13.3
Neuropathology	MTS: 57% (8) Left Hippoc. MR Signal Abn.: 7% (1=heterotopia)	MTS: 69%(9) Right TL MR Signal Abn.: 31% (4= 2 CHI, 1 encephalitis, 1 AVM)	MTS: 46%(5) Left Hippoc. MR Signal Abn.: 9% (1=idiopathic)	MTS: 50%(5) Right Hippoc. MR Signal Abn.: 30% (3= 1 encephalitis, 2 idiopathic)
	Left TL MR Signal Abn.: 29% (4= 1 CHI, 1 Reyes Syn, 2 dysplasias)		Left TL MR Signal Abn.: 36% (4= 1 ischemia, 1 CHI, 2 tumors)	
	Left TL Hypometabolism: 7% (1= anoxia)		Left TL Hypometabolism: 9% (1=idiopathic)	Right TL Hypometabolism: 20% (2= idiopathic)
Seizure Type	CPS: 72% (10)	CPS: 62%(8)	CPS: 18%(2)	CPS: 60%(6)
	CPS/SPS: 7%(1)	CPS/SPS: 15%(2)	CPS/SPS: 18%(2)	CPS/SPS: 20%(2)
	CPS[II]: 14%(2)	CPS[II]: 8%(1)	CPS[II]: 36%(4)	CPS[II]: 20%(2)
	SPS: 7%(1)	SPS: 15%(2)	CPS[¥]: 28%(3)	SPS: 0%
Medication[1]	Phenytoin 7%	Phenytoin 0%	Phenytoin 27%	Phenytoin 0%
	Keppra 57%	Keppra 25%	Keppra 55%	Keppra 38%
	Tegretal 29%	Tegretal 8%	Tegretal 0%	Tegretal 12%
	Topomax 21%	Topomax 33%	Topomax 18%	Topomax 25%
	Lamictal 21%	Lamictal 33%	Lamictal 18%	Lamictal 12%
	Trileptal 7%	Trileptal 17%	Trileptal 18%	Trileptal 25%

Abreviations: MTS=Mesial Temporal Sclerosis; CPS=Complex Partial Seizures; SG=Secondarily Generalized Seizures; SPS=Simple Partial Seizures; CHI=Child Head Injury; AVM=Arterial Venous Malformation; TL= Temporal Lobe; Abn.: Abnormalities;

[1] Medication percentiles do not sum to 100 because some patients were on multiple anticonvulsant medications.

[II] = CPS as primary type with secondary generalized seizures;

[¥] = CPS as primary type with generalized tonic-clonic seizures.

Table 2

Standardized Beta values (mean and standard deviation) computed between right and left temporal lobe ROIs, for each experimental group.

Experimental Groups	Functional Connectivity Between Left and Right Temporal Lobe ROIs (Beta Values)	
	Mean	STD
Left Unilateral	0.64	0.30
Left Bilateral	0.69	0.32
Right Unilateral	0.72	0.41
Right Bilateral	0.85	0.17
Unilateral	0.68	0.35
Bilateral	0.77	0.26
Left	0.68	0.30
Right	0.77	0.33

Abreviations: Bi=Bilateral; BA=Brodman Area; Cun=Cuneus; DFG=Medial Frontal Gyrus; IFG=Inferior Frontal Gyrus; L=Left; MFG= Middle Frontal Gyrus; PCun=Precuneus; Post=Posterior; R=Right; SPL=Superior Parietal Lobule; Temp=Temporal

Table 3

Whole brain resting state data for each Group using right and left temporal lobe ROIs as seed.

	Left Temporal ROI Seed				
	X, Y, Z	**K**	**P (FWE)**	**Location**	**Beta**
Left Unilateral	**−30, −14, −28**	**9521**	**0.0001**	**L IFG (BA 44) and post Temp. (BA 21/37)[1]**	**0.54**
	−8, −76, 16	**1473**	**0.001**	**Bi PCun (BA 18/19)**	**−0.34**
	26, 52, 24	**159**	**0.03**	**R MFG (BA 10)**	**−0.35**
Left Bilateral	null				
	Right Temporal ROI Seed				
Right Unilateral	***54, −2, −28***	***13952***	***0.0001***	***R fronto-parietal cortex and opercula*** [1]	***0.87***
	−22, −70, 40	***2453***	***0.001***	***L SPL (BA 7)***	***− 0.44***
	8, −88, 14	***1376***	***0.001***	***Bi PCun./Cun. (BA 18)***	***− 0.54***
	− 24, 48, 18	***373***	***0.001***	***L MFG (BA 10)***	***− 0.51***
	−48, 22, −6	***297***	***0.0002***	***L IFG (BA 47)***	***− 0.6***
	− 2, 32, 42	***256***	***0.0004***	***Bi DFG (BA 8)***	***− 0.6***
Right Bilateral	44, −4, −28	8768	0.0001	R ITG[1] (BA 20)	1.0
	−32, −62, 54	979	0.001	L SPL (BA 7)	0.5

Bolded data reflects findings displayed in Figures 2a and 2b. Bolded and italicized data reflects findings displayed in Figures 3a and 3b. Abreviations: Bi=Bilateral; BA=Brodman Area; ITG=Inferior Temporal Gyrus; L=Left; PCun=Precuneus; Post=Posterior; R=Right; RFG=Straight Frontal Gyrus; V Thal=Ventral Thalamus;

[1]Cluster level data includes the ROI seed itself. The brain location listed is the significant activation outside the ROI.

Table 4

Whole brain resting state data using duration of epilepsy as a covariate in the context of each of the four experimental groups.

	Left Temporal ROI Seed				
	X,Y,Z	**K**	**P (FWE)**	**Location**	**Beta**
Left Unilateral	−38, 2, −40	6011	0.0001	Post. Temporal (BA 21/37)[1]	0.58
	14, −82, 14	675	0.001	R PCun (BA 18)	−0.33
Left Bilateral	−50, −18, −30	117	0.001	L ITG (BA 20)	0.34
	−8, 20, −30	83	0.005	L RFG (BA 11)	0.31
	6, −12, 0	69	0.001	V Thal	−0.38
	Right Temporal ROI Seed				
Right Unilateral	2, −90, 10	411	0.004	Bi PCun (18)	−0.35
Right Bilateral	null				

[1]Cluster level data includes the ROI seed itself. The brain location listed is the significant activation outside the ROI.