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Diminished default mode network recruitment of the hippocampus and parahippocampus in temporal lobe epilepsy

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Abstract

Object—Functional neuroimaging has shown that the brain organizes into several independent networks of spontaneously coactivated regions during wakeful rest (resting state). Previous research has suggested that 1 such network, the default mode network (DMN), shows diminished recruitment of the hippocampus with temporal lobe epilepsy (TLE). This work seeks to elucidate how hippocampal recruitment into the DMN varies by hemisphere of epileptogenic focus.

Methods—The authors addressed this issue using functional MRI to assess resting-state DMN connectivity in 38 participants (23 control participants, 7 patients with TLE and left-sided epileptogenic foci, and 8 patients with TLE and right-sided foci). Independent component analysis was conducted to identify resting-state brain networks from control participants' data. The DMN was identified and deconstructed into its individual regions of interest (ROIs). The functional connectivity of these ROIs was analyzed both by hemisphere (left vs right) and by laterality to the epileptogenic focus (ipsilateral vs contralateral).

Results—This attempt to replicate previously published methods with this data set showed that patients with left-sided TLE had reduced connectivity between the posterior cingulate (PCC) and both the left ($p = 0.012$) and right ($p < 0.002$) hippocampus, while patients with right-sided TLE showed reduced connectivity between the PCC and right hippocampus ($p < 0.004$). After recoding ROIs by laterality, significantly diminished functional connectivity was observed between the PCC and hippocampus of both hemispheres (ipsilateral hippocampus, $p < 0.001$; contralateral hippocampus, $p = 0.017$) in patients with TLE compared with control participants. Regression analyses showed the reduced DMN recruitment of the ipsilateral hippocampus and

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parahippocampal gyrus (PHG) to be independent of clinical variables including hippocampal sclerosis, seizure frequency, and duration of illness. The graph theory metric of strength (or mean absolute correlation) showed significantly reduced connectivity of the ipsilateral hippocampus and ipsilateral PHG in patients with TLE compared with controls (hippocampus: $p = 0.028$; PHG: $p = 0.021$, after correction for false discovery rate). Finally, these hemispheric asymmetries in strength were observed in patients with TLE that corresponded to hemisphere of epileptogenic focus; 87% of patients with TLE had weaker ipsilateral hippocampus strength (compared with the contralateral hippocampus), and 80% of patients had weaker ipsilateral PHG strength.

Conclusions—This study demonstrated that recoding brain regions by the laterality to their epileptogenic focus increases the power of statistical approaches for finding interhemispheric differences in brain function. Using this approach, the authors showed TLE to selectively diminish connectivity of the hippocampus and parahippocampus in the hemisphere of the epileptogenic focus. This approach may prove to be a useful method for determining the seizure onset zone with TLE, and could be broadly applied to other neurological disorders with a lateralized onset.

Keywords

individual differences; temporal lobe epilepsy; default mode network; functional magnetic resonance imaging; graph theory; independent component analysis

The default mode network (DMN) is a network of brain regions identified by PET and fMRI as having greater activity during wakeful rest than during a task.^{19,35,37} This network has been termed the “default” network because the greater activity observed during wakeful rest is largely irrespective of task. Brain regions comprising the DMN include the PCC, ventromedial prefrontal cortex, bilateral inferior parietal lobules, bilateral dorsolateral frontal cortices, bilateral hippocampi, and bilateral parahippocampal gyri.^{11,13,33,40} The involvement of these regions suggests that the DMN assists memory consolidation, task engagement, and response preparation.⁶

Investigations of DMN properties are typically conducted during wakeful rest (resting state) to avoid confounds from task-related effort and performance.²⁴ Resting-state fMRI studies report the functional connectivity (patterns of coactivation) among network regions. Functional connectivity methods can range in complexity from reporting the bivariate correlation between two brain regions’ activities^{19,22,34} or conducting power spectrum and coherence analyses (not unlike analyses of EEG data).^{25,28,38} Altered DMN functional connectivity during wakeful rest has been observed in populations with psychiatric and neurological disorders including Alzheimer disease,^{5,20} schizophrenia,²¹ and depression.¹⁸

Previous fMRI studies suggest that functional connectivity is diminished between the hippocampus and other DMN components in patients with TLE. Examining task-related deactivations during a memory encoding paradigm, Frings and colleagues¹⁵ reported reduced connectivity between the PCC and left hippocampus in patients with left MTS. Corroborating evidence for altered hippocampal connectivity has also been reported for patients with TLE at wakeful rest.^{27,44} However, the lateralization of diminished DMN functional connectivity varies between these reports. Frings et al.¹⁵ found diminished connectivity for the left hippocampus in TLE patients with left MTS ($n = 8$), but not for the right hippocampus in TLE patients with right MTS ($n = 6$). Conversely, Zhang et al.⁴⁴ found reduced bilateral hippocampal DMN functional connectivity during wakeful rest for TLE patients with right MTS ($n = 27$) but not left MTS ($n = 25$). Furthermore, Liao et al.²⁷ recruited participants with bilateral MTS ($n = 20$) and found reduced bilateral hippocampal DMN functional connectivity during wakeful rest and reduced bilateral hippocampal structural connectivity (evident with diffusion tensor imaging as reductions in white matter density) relative to sex- and age-matched healthy controls ($n = 20$).

One approach for reconciling these contradictory findings on hemispheric differences in hippocampal recruitment with TLE is to recode hemispheres as ipsilateral or contralateral to the epileptogenic focus. Such an approach offers many advantages. First, it allows left- and right-sided TLE patient samples to be combined, thus permitting more powerful statistical inferences. Second, this recoding allows data analysis with more exploratory investigations of functional network connectivity, such as graph theory. Third, the relative recruitment of the ipsilateral and contralateral hippocampus can be compared within subjects, thus accounting for between-subject variability in functional connectivity as well as factors with an unknown influence on hippocampal connectivity, such as medications, age of epilepsy onset, and seizure frequency. This final advantage moves fMRI from group-level assessments to assessment of individual patients, thus further translating functional neuroimaging into the realm of personalized medicine.

Methods

Study Participants

Fifteen patients with TLE and 23 healthy controls underwent resting-state fMRI; demographic information for the participants is listed in Table 1. All research was conducted with prior approval of Emory University's Institutional Review Board and with each participant's written informed consent. All patients were recruited from the Emory University Comprehensive Epilepsy Center, where localization of seizure onset was determined with video-EEG monitoring. In all cases, this localization included EEG scalp monitoring, structural MRI of the brain, a PET scan, and neuropsychological testing. Two patients required invasive EEG monitoring involving the use of electrode grids and/or strips. All patients included in this study were left-hemisphere dominant for language as determined by the intracarotid amobarbital (Wada) procedure.

Healthy controls participants were carefully screened to rule out neurological or psychiatric conditions known to impact the brain, and control participants with a history of substance abuse or significant head trauma were excluded from participation. Inclusion criteria for the healthy controls included scoring within normal performance ranges on a screening measure of depression (the Beck Depression Inventory),¹ an extended mental status examination (modified Cognistat),¹⁰ and a formal measure of symptom validity testing (oral form of the Word Memory Test).¹⁷ Control participants underwent the same neuroimaging paradigm and neurocognitive tests as the patients with TLE, which lasted approximately 5–6 hours.

Less than half of the patients in the sample had MRI evidence of MTS. Because the majority of patients were not classic MTS cases, it was important to be sure that the majority of our cases experienced unilateral seizure onset given the focus on lateralized dysfunction of a neural network. Both presurgical test results and postsurgical outcome suggest that the seizures in these patients were well localized to a single hemisphere. Twelve of the 15 patients with TLE had exclusive evidence of unilateral seizure onset only using multiple diagnostic studies (PET, ictal EEG, and interictal EEG). The remaining 3 patients all exhibited bitemporal PET hypometabolism, with 1 of these patients also exhibiting bilateral interictal discharges. However, these 3 patients also had ictal EEG discharges that were clearly localized to a single hemisphere, which was used to determine lateralization. Of note, 13 of the 15 patients with TLE (including the 3 patients with bilateral PET hypometabolism) were nearly or completely seizure free at their 1-year postsurgical follow-up evaluation (Engel Class I or II), further supporting unilateral onsets. The 2 patients who did not achieve Engel Class II outcomes included 1 classic unilateral MTS case (Case 4) and 1 patient with a brain tumor (Case 11). Therefore, all of the nonlesional cases experienced significant seizure improvement. Table 2 provides a breakdown of the disease- related and demographic

variables for the TLE sample according to side of seizure onset. Table 3 provides a detailed presentation of neurodiagnostic test results for each patient with TLE.

Image Acquisition

Participants were scanned on a 3.0-T Siemens Magnetom TIM Trio scanner (Siemens Medical Solutions USA) using a 12-channel head matrix coil. The session began with 2 anatomical scans acquired at $1 \times 1 \times 1 \text{ mm}^3$ resolution with a magnetization-prepared rapid acquisition gradient echo sequence and the following parameters: 224 coronal slices, FOV 216×256 , TR 1870 msec, TE 3.06 msec, and flip angle 8° . Resting state fMRI data were acquired with an echo-planar BOLD sequence and the following parameters: 34 axial slices of 3 mm thickness, TR 2000 msec, TE 28 msec, flip angle 90° , 64×64 matrix, in-plane resolution $3.44 \times 3.44 \text{ mm}^2$, and 225 functional images, for a total duration of 7 minutes and 30 seconds. For the resting-state scan, an image of a white cross against a black background was presented by back projection into the scanner room, which participants viewed through a mirror mounted on the head coil. Participants were instructed to use the fixation cross to keep their eyes from wandering and to also keep their minds from wandering during the scan.

Region of Interest Definition

Independent component analysis was used to identify networks of coactivated brain regions during wakeful rest.^{31,32} Independent component analysis is a technique that identifies patterns of temporal covariance among variables in a large data set that varies over time (such as a functional neuroimaging data set). In functional neuroimaging, independent component analysis maps brain networks whose components have similar activity patterns across time. Because independent component analysis is a data-driven approach, it does not require a priori knowledge of functional neuroanatomy. For this reason, we chose independent component analysis over seed-based approaches to identify functional networks because this data-driven method prevents experimenter bias in the (arguably arbitrary) selection of seed regions; however, it deserves note that ROI selection with independent component analysis (either for a group or individual participants) or from anatomical templates yields comparable results.³⁰

Independent component analysis of the 23 controls was performed using the GIFT toolbox available in MATLAB (<http://icatb.sourceforge.net/>) using 2 data-reduction steps. We chose a model-order independent component analysis of 20 components and applied an Infomax independent component analysis algorithm that was repeated 20 times in Icaso3. Subject-specific spatial maps and fMRI signal time courses were estimated using the recently developed GICA3 back-reconstruction method (from the GIFT program) based on principal components analysis and projection. Prior to independent component analysis, anatomical data underwent transformation to the MNI ICBM452 brain atlas, and functional data underwent despiking, slice timing correction, deobliquing, motion correction, and spatial transformation to the MNI anatomical template (for additional details on data preprocessing, see below).

The functional MRI time series were concatenated across participants and analyzed with the following GIFT parameters and options: whitening, 20 principal components, generation of group components using the Infomax algorithm, generation of individual spatial component maps using “regular” back reconstruction, and z-score normalization of group and individual spatial maps (http://www.nitrc.org/frs/download.php/2460/v1.3h_GIFTManual.pdf).

A DMN was identified from these components for its inclusion of regions previously associated with the DMN including the PCC, medial prefrontal cortex, and bilateral parietal

cortices. The component was thresholded for figure display at $z = 1$ with a minimum cluster volume to 10 voxels (each $3 \times 3 \times 3 \text{ mm}^3$ cubes) to produce 9 distinct cluster volumes: midline PCC, midline medial prefrontal cortex, bilateral inferior parietal lobule, bilateral superior frontal cortex, left hippocampus, left PHG, and a volume encompassing both the right hippocampus and right PHG (Fig. 1). Increasing the threshold to $z = 1.101$ resolved the right hippocampal cluster into distinct hippocampus and PHG clusters. These 10 clusters were defined as ROIs by centering 6 mm radius spheres atop each cluster's center of mass (Fig. 2; Table 4).

Region of Interest Time Series Preprocessing and Extraction

Extraction of the ROI time series required additional data preprocessing, all of which was performed in AFNI,⁹ with preprocessing scripts available upon request. Anatomical scans underwent skull stripping, spatial transformation to the MNI ICBM452 brain atlas, and segmentation of gray matter, white matter, and CSF. The resting state functional series underwent (in order) despiking; slice timing correction; deobliquing; motion correction; spatial transformation to the MNI anatomical template; regression of motion parameters, global CSF signal, and global white matter signal; spatial smoothing with a 6-mm full width at half maximum Gaussian kernel; detrending; scaling to percentage signal change from baseline; and temporal filtering with a 0.01- to 0.10-Hz Fourier bandpass filter to remove physiological noise typically observed at higher frequencies, such as cardiac noise.⁸

Correlational Analysis

Region of interest activity time courses were extracted using singular value decomposition with the AFNI program 3dmaskSVD instead of a mathematical average. Singular value decomposition is preferred over a mathematical average because an average would weight all voxels of an ROI equally when calculating a mean ROI time course. However, because hippocampal MTS was evident on some patients' structural MR images, the standardized hippocampal ROIs might suboptimally cover hippocampal gray matter in patients; thus, an average would indiscriminately combine gray matter signal with non-gray matter noise. In contrast, singular value decomposition identifies voxels with similar temporal variance and weights their contribution to the ROI time series greater than voxels with dissimilar temporal variance.⁴² In other words, singular value decomposition preferentially chooses voxels with similar time series (shared variance), thereby increasing the contribution of gray matter voxels while diminishing the contribution of non-gray matter noise. We believe that singular value decomposition is superior to mathematical averages in this application because it essentially tailors the standardized ROIs to each patient's functional anatomy.

To test the hypothesis that hippocampal connectivity was reduced in epilepsy, the correlations of PCC with left hippocampus and PCC with right hippocampus were calculated for each participant, followed by 2-sample t-tests to determine if these correlations differed between controls and either left-sided TLE or right-sided TLE patients. Lateralized ROIs were then recoded from left and right ROIs to ROIs ipsilateral and contralateral to the epileptogenic focus. For control participants, 11 were randomly selected to have the right hemisphere "ipsilateral" to the nonexistent focus; the right hemisphere was "contralateral" to the focus for the remaining 11 control participants. For all analyses, ROI correlations underwent Fisher z-transformation to better approximate linearity.

Regression Analysis

These correlational analyses were followed by a linear regression analysis to assess if demographic variables influenced hippocampal recruitment into the DMN. The regression analysis was performed with the statistical software package SAS 9.2 (SAS Institute, Inc.). The dependent variable was the correlation of interest (for example, PCC and ipsilateral

hippocampus), and independent variables were patient status (0 = control, 1 = TLE), years of education, affected hemisphere (1 = right, 2 = left), age, sex (0 = male, 1 = female), handedness (0 = right, 1 = left), duration of illness (in years), seizure frequency, and presence of hippocampal sclerosis (0 = absent, 1 = present). Independent variables not significantly predicting correlation strength were removed in a stepwise fashion to improve the adjusted R^2 of the model.

Graph Theoretic Analysis

To more fully characterize the impact of TLE on the default mode, we used graph theory to model the network properties of our 10 DMN ROIs.⁷ Graph theory depicts ROIs as “nodes” and the connections (binarized correlations) between ROIs as “edges.” The following network indices were used in this study:^{29,36}

Strength—Strength is the mean absolute value of the correlation of node i to all other nodes.

Degree—Degree is the number of edges linking node i to other nodes in the network. Degree is a measure of how extensively a node is connected to the rest of the network.

Leverage Centrality—A relatively new graph theory metric, leverage centrality is the ratio of node i 's degree relative to the degree of its neighboring nodes.²⁶ A positive leverage value indicates that a node has a higher degree relative to its neighbors, which suggests that the node operates more as a “hub” by linking relatively less connected nodes together. Conversely, a negative leverage suggests a node that tends to receive information from other more connected nodes.

Clustering Coefficient—Clustering coefficient is the fraction of a node i 's neighbors that are also neighbors of each other. This metric indicates the “cliqueness” of a node, that is, the extent of integration among nodes within a neighborhood.

Betweenness Centrality—Betweenness centrality refers to the fraction of all shortest paths in a network that pass through node i . Nodes with high betweenness centrality are considered to be “hubs” that tend to link other, more segregated nodes in the network.

Calculating Graph Theory Metrics

These graph theory metrics were calculated with the Brain Connectivity Toolbox³⁶ using previously described methods.²³ In summary, correlation matrices were generated for each participant (describing the correlation between ROIs), and then binarized to produce adjacency matrices (consisting of 1s and 0s to indicate which regions were significantly correlated for each subject).¹⁰ Two-tailed t-tests were used to assess group differences in these metrics, with FDR correction for multiple comparisons in SAS. Finally, a group adjacency matrix was generated in Matlab by averaging the adjacency matrices of each group's members. To aid visualization of group differences, each group's average adjacency matrix is depicted by showing edges that exist between nodes in at least 20%, 30%, and 40% of each group's participants.

Results

Correlational Analysis

The correlations of the PCC with the hippocampus varied greatly across participants, even in healthy controls (z-transformed range for right hippocampus = -0.12 to 0.64 , left

hippocampus = -0.21 to 0.56). Correlations of the PCC with the hippocampus did not differ by hemisphere in healthy controls (mean r [PCC-right hippocampus] = 0.29 , mean r [PCC-left hippocampus] = 0.28 , paired t -test = 0.24 , $df = 21$, $p = 0.812$). The range of hippocampal correlations was similarly large for patients with TLE (right hippocampus = -0.31 to 0.30 , left hippocampus = -0.21 to 0.36).

However, differences in correlation measures were observed between the patients and controls when investigating the correlation of the PCC with the hippocampus. For patients with left-sided TLE, the correlation of the PCC with the hippocampus was significantly lower than controls for both the left hippocampus (mean r [controls] = 0.270 , mean r [patients] = 0.017 , 2-tailed $t = 2.71$, $df = 27$, $p = 0.012$) and right hippocampus (mean r [controls] = 0.279 , mean r [patients] = 0.008 , 2-tailed $t = 3.47$, $df = 27$, $p < 0.002$). For patients with right-sided TLE, the correlation of the PCC with the hippocampus was significantly lower than controls for the right hippocampus (mean r [controls] = 0.279 , mean r [patients] = 0.080 , 2-tailed $t = 3.11$, $df = 28$, $p < 0.004$) but not the left hippocampus (mean r [controls] = 0.270 , mean r [patients] = 0.212 , 2-tailed $t = 0.77$, $df = 28$, $p = 0.448$). More profound group differences were apparent after recoding the right and left ROIs into ROIs ipsilateral or contralateral to the TLE focus. The mean correlation of the ipsilateral hippocampus with the PCC was significantly lower for TLE patients (mean $r = 0.051$) than control participants (mean $r = 0.280$; 2-tailed $t = 3.68$, $df = 35$, $p < 0.001$). Likewise, the mean correlation of the contralateral hippocampus with the PCC significantly differed between patients (mean $r = 0.116$) and controls (mean $r = 0.284$, 2-tailed $t = 2.51$, $df = 35$, $p = 0.017$).

The graph theory analyses also indicated reduced functional connectivity of the PHG, so the correlational analyses were replicated for the right PHG, left PHG, ipsilateral PHG, and contralateral PHG. For patients with left-sided TLE, the correlation between the PCC and PHG was significantly lower than controls for both the left PHG (mean r [controls] = 0.323 , mean r [patients] = -0.081 , 2-tailed $t = 5.21$, $df = 27$, $p < 0.001$) and right PHG (mean r [controls] = 0.286 , mean r [patients] = 0.091 , 2-tailed $t = 2.07$, $df = 27$, $p = 0.048$). For patients with right-sided TLE, the correlation of the PCC with the PHG was significantly lower than controls for the right PHG (mean r [controls] = 0.286 , mean r [patients] = 0.069 , 2-tailed $t = 2.84$, $df = 28$, $p = 0.008$) but not the left PHG (mean r [controls] = 0.323 , mean r [patients] = 0.225 , 2-tailed $t = 1.40$, $df = 28$, $p = 0.171$). After recoding the ROIs by laterality to the epileptogenic focus, the correlation between the PCC and PHG was significantly reduced for both the ipsilateral PHG (mean r [controls] = 0.307 , mean r [patients] = -0.001 , 2-tailed $t = 5.18$, $df = 35$, $p < 0.001$) and the contralateral PHG (mean r [controls] = 0.323 , mean r [patients] = 0.162 , 2-tailed $t = 2.11$, $df = 35$, $p = 0.042$) in patients with TLE relative to controls.

Linear Regression

The Appendix summarizes the linear regression results. The correlation between the PCC and ipsilateral hippocampus was significantly predicted by 3 variables: patient status ($p = 0.001$), education ($p = 0.067$), and age ($p = 0.040$). Sex and hippocampal sclerosis did not significantly predict a PCC-ipsilateral hippocampus correlation. The overall fit of the model (adjusted R^2) increased when removing hippocampal sclerosis as a predicting variable but decreased when removing sex; thus, sex was retained despite its nonsignificant contribution to the model. Patient status was the most significant predictor and had the greatest impact on the PCC-ipsilateral hippocampus correlation; controlling for other factors, the correlation was 0.203 lower for patients than control participants. Age and education had a more modest impact, with the correlation increasing by 0.005 and 0.021 , respectively, for each year of age or year of education. The model explained 38.8% of variance in the correlation.

The correlation between the PCC and ipsilateral PHG was significantly predicted by 2 variables: patient status ($p < 0.0001$) and education ($p = 0.028$). This model explained 48.1% of the variance in the correlation—the most variance explained of the 4 regression analyses conducted. The PCC–ipsilateral PHG correlation was 0.294 less for patients than controls and increased by 0.025 for each year of education. All other variables were nonsignificant and did not improve model fit with their inclusion.

The regression analyses for contralateral ROIs explained far less variance: 15.8% of variance for PCC–contralateral hippocampus and 17.0% for PCC–contralateral PHG. Patient status was a significant predictor for both linear regressions, with correlations approximately 0.15 lower for patients than controls. For both regressions, education and sex were nonsignificant predictors that increased the model fit (adjusted R^2 value) when included. All other variables were nonsignificant and did not improve model fit when included.

Graph Theory

Table 5 provides uncorrected p values for the 5 graph theory metrics by ROI. For patients with TLE, hemispheric differences in the graph theory strength parameter corresponded with hemisphere of seizure onset. Contralateral hippocampus strength was greater than ipsilateral hippocampus strength for 13 (87%) of 15 patients with TLE, and contralateral PHG strength was greater than ipsilateral PHG strength for 12 (80%) of 15 patients with TLE. These outcomes suggest hemispheric differences in strength may be a biomarker for hemispheric localization of epileptogenic foci.

After FDR correction for multiple comparisons, significant group differences were only observed for the strength of the ipsilateral hippocampus (control $\mu = 0.300$, patient $\mu = 0.205$, Wilcoxon rank sum = 195, $z = 2.77$, p [uncorrected] = 0.006, $p_{FDR} = 0.028$) and strength of the ipsilateral PHG (control $\mu = 0.349$, patient $\mu = 0.222$, Wilcoxon rank sum = 182, $z = 3.17$, p [uncorrected] = 0.002, $p_{FDR} = 0.021$). The Wilcoxon rank-sum test was selected because the correlation distribution cannot be assumed to be normal; a follow-up t -test analysis yielded more significant results. Linear regression analyses showed that the strength of each ROI was only predicted by patient status, with no other demographic variable significantly predicting strength; as such, the rank-sum tests above are entirely explained by patient status. Strength did not significantly differ between groups for any other ROI, nor did any other metric (degree, clustering, betweenness centrality, or leverage) differ between groups for any ROI.

Figure 3 graphically depicts the functional connectivity of the DMN for both groups at 3 different thresholds (that is, only depicting edges that exist in 20%, 30%, and 40% of each sample). The most commonly cited components of the DMN (PCC, medial prefrontal cortex, ipsilateral parietal lobule, and contralateral parietal lobule) are interconnected with one another across all thresholds and both groups. In contrast, the ipsilateral hippocampus and parahippocampus show greater isolation from the rest of the DMN for patients relative to control participants. The extent of these regions' isolation increases with increasing threshold and is especially evident at 40%, where only the contralateral hippocampus and parahippocampus interact with the rest of the network.

Discussion

We demonstrate reduced connectivity in mesial temporal structures in presurgical patients with TLE. Both the hippocampus and parahippocampus are less connected to the DMN. Connectivity is reduced for structures both ipsilateral and contralateral to the surgical site, but the effect is greater for the ipsilateral hippocampus and PHG.

Benefit of Incorporating Laterality Into Neuroimaging Analyses

We propose a simple yet novel approach for recoding ROIs by their laterality to an anatomical or neurological feature. Our approach allows two distinct samples (patients with left-sided and right-sided epileptogenic foci) to be analyzed as a single sample, thereby increasing the statistical power of analyses and permitting sophisticated methods such as graph theoretic analysis. Our approach resolves ongoing controversy over the recruitment of the hippocampus into the DMN in patients with TLE. Although the bivariate correlations between the PCC and hippocampus reported here add to the conflict of previous reports,^{15,27,44} graph theory shows reduced functional connectivity only for the hippocampus and parahippocampus ipsilateral to the epileptogenic focus. Because strength is a mean of correlations between an ROI and all other ROIs in the network, we believe it is more representative of an ROI's recruitment into the network than the simple bivariate correlation between 2 ROIs.

Our use of graph theory not only confirmed expectations for reduced ipsilateral hippocampal connectivity but also provided unanticipated evidence of reduced ipsilateral parahippocampal connectivity, illustrating a broader impact upon ipsilateral temporal lobe function in TLE. Likewise, TLE has been shown to impact the structural connectivity of ipsilateral structures beyond the epileptic hippocampus.³⁹ It deserves note that our independent component analysis initially clustered the right hippocampus and parahippocampus into a single cluster with 2 activity peaks centered upon each region. While we may be the first to specifically report decreased DMN recruitment of the ipsilateral parahippocampus, previous investigations (2 of which also used independent component analysis) may have similarly clustered the hippocampus and parahippocampus together due to the regions' close proximity and related functionality.

Our analyses of right and left hippocampal DMN connectivity did not resolve the previously reported literature findings; on the contrary, we introduce additional contradicting evidence. Whereas Zhang et al.⁴⁴ reported reduced bilateral hippocampal DMN connectivity for TLE patients with right-sided foci (as evidenced by right hemisphere MTS), we report reduced bilateral hippocampal connectivity for TLE with left-sided foci and reduced unilateral (ipsilateral) hippocampal connectivity for TLE patients with right-sided foci. An important caveat is that the small sample sizes of these studies (including this one) are more likely to result in spurious statistical findings.⁴³ However, this further underscores the value of recoding ROIs by laterality to improve sample size and thus statistical power.

Previous investigations used hippocampal sclerosis as an indicator for TLE. Because fewer than half of our TLE patients had evidence of sclerosis, we used linear regression to assess the impact of sclerosis and other clinical and demographic factors upon hippocampal connectivity. For all regression models, patient status had the greatest impact (in both magnitude and significance) upon the bivariate hippocampal correlations with the PCC, with greater impact for the ipsilateral hippocampus and PHG than the contralateral. Hippocampal sclerosis was not a significant predictor for any regression, suggesting that sclerosis—while a consequence of TLE—is not itself responsible for decreased functional connectivity. Despite our best attempts to control for demographic variables between groups, education was significantly different between patient groups ($p = 0.02$, with right-sided TLE patients having approximately 3 years more education than left-sided TLE patients). Although education improved model stability for all regression analyses, education and age were more modest predictors than patient status, thus confirming that the decreased functional connectivity of the ROIs is primarily caused by patient status (having TLE).

The absence of an observed effect of hippocampal sclerosis on connectivity suggests that it is the presence of seizures, rather than an observable structural lesion, that is associated with

a decrease in connectivity. How seizures disrupt this normal interaction and whether this is a marker of disruption of function (for example, memory) remains to be determined. Such alterations of structure and function would be viewed as akin to known reorganization of language and memory networks,¹⁶ possibilities that should be explored with much larger sample sizes.

Diminished (but Not Disrupted) Hippocampal DMN Connectivity With TLE

The role of the medial temporal lobe (including the hippocampus and parahippocampus) in the DMN remains unclear. Activity of the PCC has been consistently shown to be more weakly correlated with the hippocampal formation than other DMN components, such as medial prefrontal and inferior parietal cortices.^{2,4,12,14} This weaker recruitment of the medial temporal lobe into the DMN has been suggested to reflect either a subnetwork or interacting network,^{4,14} possibly carrying out independent yet concurrent functions. While at least 1 study has shown lateralization differences in PCC and hippocampal connectivity,¹⁴ these findings are largely unreported in the literature and were not observed for the healthy controls acquired in this study. Nonetheless, these points underscore the need for large-sample ($n > 100$) healthy control subject analyses of resting state connectivity, such as those proposed through the Human Connectome Project.

No other graph properties (degree, leverage, clustering, or betweenness centrality) significantly differed between patients and controls. We can infer from this diminished but not disrupted DMN connectivity in TLE, suggesting that while the strength of ipsilateral hippocampal and parahippocampal connectivity decreases with epilepsy, the functional architecture of the DMN remains the same. Bearing this caveat in mind, Fig. 3 depicts the functional network by group at varying thresholds. The hippocampus and parahippocampus appear more isolated from the rest of the network in patients compared with controls, especially as the threshold increases for participants showing a significant correlation between regions. At a threshold of 40% (limiting connections only to those edges existing in at least 40% of the sample), the hippocampal/parahippocampal complex is almost completely isolated from the rest of the network in patients, joined only by edges connecting the contralateral hippocampus to the medial prefrontal cortex and the contralateral parahippocampal gyrus to the PCC and ipsilateral parietal lobule.

Again, while no significant difference in network characteristics exists, a trend is clearly evident for isolated hippocampal function with TLE. Other groups have reported similar decreases in resting-state connectivity of temporal lobe structures in patients with TLE. Bettus et al.³ reported decreased resting-state functional connectivity for the entorhinal cortex and anterior hippocampus in patients with TLE relative to healthy controls. Although these decreases were observed bilaterally, they were significantly more prominent in the hemisphere ipsilateral to the epileptogenic focus. Furthermore, decreased local field potentials have been reported for seizure-generating epileptic brain regions.⁴¹ These findings, in conjunction with our own, suggest that the affected hippocampus becomes isolated from brain networks. This hippocampal isolation may represent an adaptive cortical reorganization of the brain's connectivity to minimize the impact of seizures upon the rest of the brain. Alternately, this isolation may result from subclinical damage to hippocampal and parahippocampal neurons secondary to seizure activity, perhaps as a precursor to clinically observable sclerosis. These explanations are not mutually exclusive and warrant further investigation.

Interestingly, while we report no significant changes in contralateral hippocampal connectivity with other DMN regions, Bettus et al.³ found significantly increased functional connectivity of the contralateral hippocampus and amygdala with other temporal lobe structures. These findings together suggest a shift in internetwork dynamics, with selective

alteration of the contralateral hippocampus's involvement in 1 or more networks. Future work will explore the impact of TLE upon hippocampal connectivity across multiple brain networks.

Identifying Epileptogenic Foci Through Laterality Differences

Finally, we reported asymmetrically reduced strength of the ipsilateral hippocampus and PHG in patients relative to the contralateral hippocampus and PHG, which may be a valuable biomarker for identifying the lateralization of epileptogenic foci from resting-state fMR images. Because this asymmetrical reduction in ipsilateral hippocampal and PHG functional connectivity appears to be independent of hippocampal sclerosis, this approach may aid clinical decision-making in cases in which standard approaches for determining the lateralization of epileptogenic foci are inconclusive. Similar arguments have been promoted by Bettus et al.³ for temporal lobe networks; while they did not explicitly use the graph theory metric of strength, they report more numerous decreases in hippocampal connectivity for the affected hemisphere, which would correspond to decreased strength. Examining alterations in resting state connectivity may prove complementary to PET or SPECT for use in localization of seizure onset and has the advantages of not using ionizing radiation, and representing a brief add-on sequence for an already obtained structural scan. Future work will use a larger patient sample to compare this graph theoretic approach for localizing epileptogenic foci against existing clinical methods.

Caveats and Limitations

As with most neuroimaging investigations, the primary limitation of this study is its relatively small sample size. A larger sample is needed to fully model variables associated with lateralized brain function (such as language or handedness).

Our inclusion of TLE patients with and without MTS is more heterogeneous than prior studies, and this represents the surgical population in practice. This inclusion increases the likelihood that we would include some patients with bilateral or less well-localized presentations. However, our results nevertheless achieved statistical significance. As all of our nonlesional TLE cases achieved a very good seizure outcome (at 1 year postoperatively), it appears that they were correctly identified as lateralized epilepsy during the clinical presurgical evaluation.

Conclusions

We have proposed a method for investigating lateralized differences in brain function that resolves ongoing controversy over reduced functional connectivity of the hippocampus with TLE. While the impact of left versus right hemisphere TLE on DMN functional connectivity remains unclear, our recoding of brain regions into ipsilateral or contralateral to the epileptogenic focus provides indisputable evidence for reduced ipsilateral hippocampal and parahippocampal connectivity with TLE. This methodological approach paves the way for statistical analyses such as graph theory for exploratory assessments of brain function in epilepsy, which would otherwise be limited by the inability to combine left- and right-sided patient samples. With the increasing availability of resting-state fMRI data in epilepsy patients, these methods will further expand the translational impact of functional neuroimaging for patient diagnosis and prognosis.

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Abbreviations used in this paper

df	degrees of freedom
DMN	default mode network
EEG	electroencephalography
FDR	false discovery rate
fMRI	functional MRI
HPC	hippocampus
MNI	Montreal Neurological Institute
MTS	mesial temporal sclerosis
PCC	posterior cingulate cortex
PHG	parahippocampal gyrus
ROI	region of interest
TLE	temporal lobe epilepsy

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Appendix

Regression analysis of activity correlation between PCC and ipsilateral HPC*

Source	DF	Sum of Squares	Mean Square	F-Score	p Value
model	4	0.765	0.191	6.71	0.001
error	32	0.912	0.029		
corrected total	36	1.677			

* $R^2 = 0.456$, adjusted $R^2 = 0.388$. DF = degrees of freedom.

Variables contributing to regression analysis of correlation between PCC and ipsilateral HPC

Variable	DF	Parameter Estimate	SEM	t-Score	p Value
intercept	1	−0.307	0.207	−1.49	0.147
patient	1	−0.203	0.057	−3.54	0.001
education	1	0.021	0.011	1.90	0.067
age	1	0.005	0.002	2.14	0.040
female	1	0.110	0.059	1.86	0.071

Regression analysis of activity correlation between PCC and ipsilateral PHG*

Source	DF	Sum of Squares	Mean Square	F-Score	p Value
model	2	0.994	0.497	17.65	0.0001
error	34	0.958	0.028		
corrected total	36	1.951			

* $R^2 = 0.509$, adjusted $R^2 = 0.481$.

Variables contributing to regression analysis of correlation between PCC and ipsilateral PHG

Variable	DF	Parameter Estimate	SEM	t-Score	p Value
intercept	1	-0.083	0.174	-0.48	0.637
patient	1	-0.294	0.057	-5.21	0.0001
education	1	0.025	0.011	2.29	0.028

Regression analysis of activity correlation between PCC and contralateral HPC*

Source	DF	Sum of Squares	Mean Square	F-Score	p Value
model	3	0.372	0.124	3.24	0.034
error	33	1.261	0.038		
corrected total	36	1.633			

* $R^2 = 0.228$, adjusted $R^2 = 0.158$.

Variables contributing to regression analysis of correlation between PCC and contralateral HPC

Variable	DF	Parameter Estimate	SEM	t-Score	p Value
intercept	1	-0.091	0.217	-0.42	0.679
patient	1	-0.157	0.066	-2.39	0.023
education	1	0.022	0.013	1.65	0.108
female	1	0.066	0.068	0.96	0.343

Regression analysis of activity correlation between PCC and contralateral PHG*

Source	DF	Sum of Squares	Mean Square	F-Score	p Value
model	3	0.484	0.161	3.46	0.027
error	33	1.539	0.047		
corrected total	36	12.023			

* $R^2 = 0.239$, adjusted $R^2 = 0.170$.

Variables contributing to regression analysis of correlation between PCC and contralateral PHG

Variable	DF	Parameter Estimate	SEM	t-Score	p Value
intercept	1	−0.189	0.239	−0.79	0.436
patient	1	−0.148	0.073	−2.04	0.049
education	1	0.028	0.014	1.96	0.059
female	1	0.120	0.075	1.59	0.122

Fig. 1.

Functional MR images showing the DMN in healthy controls. Midline structures, including the medial prefrontal cortex and PCC, are observed along with bilateral hippocampal and parahippocampal regions. Independent component analysis was conducted on the healthy controls' resting-state fMRI data to generate 20 components. The component representing the DMN was thresholded to include voxels with a significant contribution to the component time course ($z \geq 1.00$ and 10 voxels) and over-laid atop the MNI ICBM452 structural brain atlas provided with the AFNI software package. Images are displayed in neurological convention (left side is on the left of the axial slice).

Fig. 2.

Default mode network ROIs. The ROIs were defined as 6 mm radius spheres centered on the center of mass for each of the 10 ROI clusters generated from the independent component analysis in Fig. 1 and described in Table 4. The ROIs were used in connectivity analysis across groups. Images are displayed in neurological convention. MPFC = medial prefrontal cortex; L PAR = left inferior parietal lobule; R PAR = right inferior parietal lobule; L HPC = left hippocampus; R HPC = right hippocampus; L PHG = left PHG; R PHG = right PHG; L SFC = left superior frontal cortex; R SFC = right superior frontal cortex.

Fig. 3.

Graph theory depiction of DMN connectivity in healthy controls and patients with TLE. There is less connectivity of the ipsilateral hippocampus (HPC_I) and contralateral hippocampus (HPC_C) to the rest of network. The strength of connectivity of these regions to the PCC was significantly less in the patient group than the control group. Each subject's ROI correlation matrix was binarized into an adjacency matrix describing the presence or absence of a connection (edge) between 2 ROIs (nodes). Lines depict edges present in the adjacency matrices at different population thresholds (that is, at least 20%, 30%, and 40% of each sample). PHG_I = ipsilateral PHG; PHG_C = contralateral PHG; MPFC = medial prefrontal cortex; PAR_I = ipsilateral inferior parietal lobule; PAR_C = contralateral inferior parietal lobule; SFC_I = ipsilateral superior frontal cortex; SFC_C = contralateral superior frontal cortex.

TABLE 1

Demographic variables for the healthy control and epilepsy study participants*

Variable	Healthy Controls (n = 23)	TLE Patients (n = 15)	t-Score	χ^2	p Value
mean age $\pm$ SD (yrs)	39.1 $\pm$ 13.2	35.5 $\pm$ 12.0	0.85	NA	0.40
mean education $\pm$ SD (yrs)	15.4 $\pm$ 2.1	14.9 $\pm$ 3.6	0.63	NA	0.37
males/females	9/14	5/10	NA	0.13	0.72
lt/rt handedness	2/21	5/10	NA	3.67	0.06
African American/Caucasian	5/18	4/11	NA	0.12	0.73

* NA = not applicable.

Demographic and disease/seizure-related variables of the epilepsy study participants according to side of seizure onset

TABLE 2

Variable	Left-Sided TLE (n = 7)	Right-Sided TLE (n = 8)	t-Score	χ^2	p Value
mean age $\pm$ SD (yrs)	31.9 $\pm$ 10.7	38.6 $\pm$ 12.8	-1.10	NA	0.29
mean education $\pm$ SD (yrs)	12.9 $\pm$ 1.7	16.6 $\pm$ 3.2	-2.77	NA	0.02*
mean seizure onset $\pm$ SD (yrs)	13.6 $\pm$ 11.3	7.4 $\pm$ 5.5	1.39	NA	0.19
mean no. of AEDs $\pm$ SD	2.43 $\pm$ 0.53	1.9 $\pm$ 0.64	1.79	NA	0.10
mean no. seizures/month $\pm$ SD	11.2 $\pm$ 21.5	13.4 $\pm$ 12.2	-0.23	NA	0.82
males/females	2/5	3/5	NA	0.13	0.71
MTS	2/7 patients	4/8 patients	NA	0.71	0.40

* Significant group difference (p = 0.05). Abbreviation: AEDs = antiepileptic drugs.

TABLE 3

Description of brain dysfunction apparent in preoperative seizure patients based on neuroimaging and video-EEG monitoring

Case No.	Region of Brain Dysfunction *	Seizure Origin	EEG Findings		Basis of Group Assignment	
			Ictal [†]	Interictal	MRI Results	PET Scan Results
1	ant lt	idiopathic	ant lt	lt TL spikes	normal	lt mesial TL hypometabolism
2	ant rt	idiopathic	ant rt	rt TL sharp waves	rt MTS	rt mesial and lateral TL hypometabolism
3	ant lt	postinfectious	ant lt	no discharges	lt MTS	bilat hypometabolism (lt > rt)
4	ant lt	posttraumatic	ant lt	lt ant TL spikes	lt MTS	NA
5	ant rt	idiopathic	ant rt	rt TL sharp waves	normal	slight hypometabolism of rt anterior TL
6	ant rt	postinfectious	ant rt	no discharges	rt MTS	rt mesial TL hypometabolism
7	ant rt	idiopathic	ant rt	rt basal TL spikes	normal	rt TL & rt parietal hypometabolism; mild hypometabolism of lt TL
8	ant rt	idiopathic	ant rt	rt TL sharp & slow wave activities	rt MTS	NA
9	ant rt	right TL tumor	ant rt	frequent rt anterior TL sharp waves during Stage II sleep	nonenhancing subcentimeter lesion in the rt TL	rt TL hypometabolism, particularly observed in medial region
10	ant lt	idiopathic	ant lt	lt TL sharp waves	normal	lt TL and FL hypometabolism
11	ant rt	right TL tumor	ant rt	bilat TL sharp waves (rt > lt)	1.2-cm mass lesion involving rt parahippocampus/no MTS	bilat TL hypometabolism (rt > lt)
12	ant rt	posttraumatic	ant rt	occasional rt TL sharp waves	rt MTS, mild generalized volume loss, & minimal nonspecific white matter changes (likely microvascular)	rt TL hypometabolism
13	ant lt	posttraumatic	ant lt	lt TL sharp waves	normal	subtle lt TL hypometabolism
14	ant lt	idiopathic	ant lt	no discharges	normal	PET (NA); SPECT revealed decreased tracer uptake in lt TL
15	ant lt	idiopathic	ant lt	occasional 5-7 Hz slowing of the posterior dominant rhythm	lt MTS	subtle lt TL hypometabolism

* In the temporal lobe. Abbreviations: ant = anterior; FL = frontal lobe; TL = temporal lobe.

[†] Related to temporal lobe discharges.

TABLE 4

Montreal Neurological Institute coordinates for ROIs*

ROI	Label	Cluster Size	Center of Mass			Peak Activation		
			x	y	z	x	y	z
1	posterior cingulate	1305	-1.4	-55.7	19.9	-1.5	-55.5	14.5
2	inferior parietal lobule (rt)	510	43.2	-67.5	26.1	46.5	-70.5	26.5
3	inferior parietal lobule (lt)	440	-38.8	-72.7	29.2	-37.5	-76.5	32.5
4	medial prefrontal cortex	293	0.2	51.3	2.9	1.5	55.5	2.5
5	superior frontal cortex (rt)	247	24.2	25.1	52.7	25.5	28.5	53.5
6	superior frontal cortex (lt)	227	-24.9	23	53.8	-25.5	22.5	53.5
7	parahippocampal gyrus (lt)	33	-25.2	-34.3	-12.3	-25.5	-34.5	-12.5
8	hippocampus (rt)	28	21	-14.6	-15.3	19.5	-16.5	-15.5
9	hippocampus (lt)	24	-20.7	-14.3	-14.5	-19.5	-16.5	-12.5
10	parahippocampal gyrus (rt)	17	25.5	-30.5	-13.9	25.5	-31.5	-12.5

* Cluster size given in $3 \times 3 \times 3 \text{ mm}^3$ voxels; center of mass and peak activation are given in MNI coordinates obtained from the AFNI ICBM452 brain template.

TABLE 5
Uncorrected p values for group comparisons (TLE patients vs controls) of graph theory metrics*

Metric [†]	HPCI	HPCC	PHGI	PHGC	MPFC	PCC	PARI	PARC	SFCI	SFCC
degree	0.377	0.610	0.033	0.546	0.769	0.963	0.757	0.654	0.072	0.901
clustering	0.641	0.421	0.146	0.228	0.466	0.546	0.189	0.150	0.114	0.988
betweenness centrality	0.529	0.529	0.476	0.395	0.609	0.676	0.632	0.664	0.271	0.938
leverage	0.467	0.841	0.067	0.362	0.745	0.841	0.938	0.449	0.467	0.610
strength	0.006 [‡]	0.210	0.002 [‡]	0.037	0.632	0.506	0.722	0.914	0.865	0.362

* HPCI = ipsilateral hippocampus; HPCC = contralateral hippocampus; PHGI = ipsilateral PHG; PHGC = contralateral PHG; MPFC = medial prefrontal cortex; PARI = ipsilateral parietal lobule; PARC = contralateral parietal lobule; SFCI = ipsilateral superior frontal cortex; SFCC = contralateral superior frontal cortex.

[†] Each metric is described in the text.

[‡] Significantly lower (p = 0.05 after FDR correction) in patients compared with controls.