Epilepsy & Behavior 101 (2019) 106585

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Network connectivity separate from the hypothesized irritative zone correlates with impaired cognition and higher rates of seizure recurrence

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ARTICLE INFO

Article history:
Received 1 September 2019
Revised 20 September 2019
Accepted 20 September 2019
Available online 4 November 2019

Keywords:
Temporal lobe epilepsy
Neuropsychology
Functional networks
Contralateral hemisphere
Extratemporal

ABSTRACT

Introduction: Surgery remains an essential option for the treatment of medically intractable temporal lobe epilepsy (TLE). However, only 66% of patients achieve postoperative seizure freedom, perhaps attributable to an incomplete understanding of brain network alterations in surgical candidates. Here, we applied a novel network modeling algorithm and measured key characteristics of epileptic networks correlated with surgical outcomes and objective measures of cognition.

Methods: Twenty-two patients were prospectively included, and relevant demographic information was attained. Resting state functional magnetic resonance imaging (rsfMRI) and electroencephalography (EEG) data were recorded and preprocessed. Using our novel algorithm, patient-specific epileptic networks were mapped preoperatively, and geographic spread was quantified. Global functional connectivity was also determined using a volumetric functional atlas. Neuropsychological pre- and postsurgical raw and standardized scores obtained blinded to epileptic network status. Key demographic data and features of epileptic networks were then correlated with surgical outcome using Pearson's product–moment correlation.

Results: At an average follow-up of 18.4 months, 15/22 (68%) patients were seizure-free. Connectivity was measured globally using a functional 3D atlas. Higher mean global connectivity correlated with worse scores in preoperative neuropsychological testing of executive functioning (Ruff Figural Fluency Test [RFFT]-ER; $R = 0.943$, $p = 0.005$). A higher ratio of highly correlated connections between regions of interest (ROIs) in the hemisphere contralateral to the seizure onset correlated with impairment in executive functioning (RFFT-ER; $R = 0.943$, $p = 0.005$). Higher numbers of highly correlated connections between ROIs in the contralateral hemisphere correlated with impairment in both short- and long-term measures of verbal memory (Rey Auditory Verbal Learning Test Trials 6, 7 [RAVLT6, RAVLT7]; $R = -0.650$, $p = 0.020$, $R = -0.676$, $p = 0.030$). Epilepsy networks were modeled in each patient, and localization of the epilepsy network in the bitemporal lobes correlated with lower scores in neuropsychological tests measuring verbal learning and short-term memory (RAVLT6; $R = -0.671$, $p = 0.024$). Higher rates of seizure recurrence correlated with localization of the epilepsy network bitemporally ($R = -0.542$, $p = 0.014$), with the stronger correlation found with localization to the contralateral temporal lobe from side of surgery ($R = -0.530$, $p = 0.016$).

Conclusion: Increased connectivity contralateral to seizure onset and epilepsy network spread in the bitemporal lobes correlated with lower measures of executive functioning and verbal memory. Epilepsy network localization to the bitemporal lobes, in particular, the contralateral temporal lobe, is associated with higher rates of seizure recurrence. These findings may reflect network-level disruption that has infiltrated the contralateral hemisphere and the bitemporal lobes contributing to impaired cognition and

Abbreviations: (^{18}F-FDG) PET, ^{18}Fluoro-2-deoxyglucose positron emission tomography; BOLD, blood oxygenation level-dependent; BNT, Boston Naming Test; COWAT-FAS, Controlled Oral Word Association Test; ECoG, electrocorticography; EEG, electroencephalography; MNI, Montreal Neurological Institute; rsfMRI, resting state functional MRI; RAVLT6, Rey Auditory Verbal Learning Test, Trial 6; RAVLT7, Rey Auditory Verbal Learning Test, Trial 7; RFFT, Ruff Figural Fluency Test-unique designs; TLE, temporal lobe epilepsy; FSIQ, Wechsler Adult Intelligence Scale-4th Ed. — Full Scale Intelligence Quotient; LM-I, Wechsler Memory Scale-4th Ed., Logical Memory Immediate recall subtest; LM-II, Wechsler Memory Scale-4th Ed., Logical Memory Delayed recall subtest; VR-I, Wechsler Memory Scale-4th Ed., Visual Reproduction Immediate Recall subtest; VR-II, Wechsler Memory Scale-4th Ed., Visual Reproduction Delayed Recall subtest.

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https://doi.org/10.1016/j.yebeh.2019.106585

relatively worse surgical outcomes. Further identification of network parameters that predict patient outcomes may aid in patient selection, resection planning, and ultimately the efficacy of epilepsy surgery.

1. Introduction

1.1. Functional outcomes of long-term epilepsy

Epilepsy is a major neurological health concern, with a global prevalence of 0.5–1% [1]. Approximately 20–30% of patients with epilepsy are refractory to pharmaceutical intervention [2]. In cases of medically refractory epilepsy, surgery may be warranted in accordance with imaging work up using magnetic resonance imaging (MRI) and electroencephalography (EEG). However, even then, only two-thirds of surgical candidates achieve postoperative seizure freedom. Taken together, this means one-sixth or 17% of patients with epilepsy never achieve seizure freedom by surgical or medical means. Intractable epilepsy has been shown to be associated with a decline in executive skills, memory, and cognitive function [3,4]. Changes in cortical connectivity and atrophy of neural substrates, particularly the hippocampus, are also seen in the ipsilateral epileptic cortex in patients with medically refractory temporal lobe epilepsy (TLE) [3]. These alterations in cortical connectivity can potentially give rise to comorbid disorders such as mesial temporal sclerosis (MTS) in an estimated 30.5 to 45% of all cases [5,6].

1.2. Network connectivity changes in TLE

Network mapping involves measuring cortical and subcortical activity over time and interpreting the data using a combination of analytical and graph-theory mapping techniques to evaluate causality and correlativity between disease pathology and target brain areas. Alterations in extratemporal brain network connectivity are evident in patients with intractable TLE, which may contribute to cognitive decline [7]. While the primary pathology of TLE is MTS, the effect of TLE may progress to structural changes of extratemporal brain regions, which may be linked to changes in functional connectivity [8–10]. Maccotta et al. showed a decrease in interhemispheric connectivity in patients with epilepsy and an increase in intrahemispheric connectivity ipsilateral to the seizure onset using functional MRI (fMRI). There was also a decreased connectivity of specific extratemporal structures including the parahippocampal gyrus, hippocampal head, and medial frontal cortex ipsilateral to the epileptogenic focus with their contralateral homologs [11]. Atrophy of a given region may result in increased internal coherence of remaining cell populations resulting in improved correlation of other brain regions. Similar studies by Bonihla et al. show a functional reorganization of the limbic system that is associated with TLE [12]. Indeed, recently, several studies employing resting state functional MRI (rsfMRI) have also shown diffuse extratemporal alterations in default-mode network (DMN) connectivity in the cingulate cortex correlating with episodic memory impairments [13–15]. Finally, Doucet et al. has shown that when extratemporal functional connectivity changes are coupled with reductions in gray matter volume deficits in episode memory recall result [16]. Thus, there is substantial evidence to suggest that diffuse alterations in functional connectivity in TLE may contribute to progressive cognitive decline. However, few studies have been performed that employ a multimodal network mapping approach to correlate preoperative network characteristics with surgical outcome.

1.3. Approaches to network mapping in epilepsy

In the aforementioned studies, either scalp EEG or, more recently, rsfMRI was the imaging modality of choice. Noninvasive scalp EEG is unrivaled in temporal resolution for the detection of epileptiform discharges but suffers from a lack of spatial resolution due to interference from the skin, bone, brain, and cerebrospinal fluid. On the contrary, while rsfMRI has been used to great effect in the measurement of spatial alterations in epileptic networks, it suffers from poor temporal resolution needed to localize ictal and interictal activity. Integrating data from both modalities effectively allows for optimal mapping of epileptic networks while minimizing the drawbacks of each modality. Recently, we developed an algorithm that combines data from both scalp EEG and rsfMRI to create a 3D network map of each patient. This modeling algorithm allowed for a better definition of global brain network connectivity and evaluation of network level changes between an epileptic and nonepileptic brain [17].

1.4. Objective

Using our novel network modeling algorithm, we conducted a prospective observational study to identify correlations between network connectivity, surgical outcomes, and cognitive function in twenty-two patients with medically intractable TLE.

2. Materials and methods

2.1. Patient demographics

All reported data followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational trials. Epileptic networks were modeled in twenty-two patients with TLE. The patients included in this study represent a consecutive series of twenty-two patients with TLE who signed consent and agreed to participate in this study (Table 1). Each patient underwent a Phase I presurgical workup for epilepsy surgery including the following: MRI, long-term EEG monitoring (LTM), Wada testing, ^{18}Fluoro-2-deoxyglucose positron emission tomography ((^{18}F-FDG) PET), and

Table 1
Demographics.

Patient number	Gender	Age at surgery	Surgery side	Seizure-free
1	Male	26	Right	No
2	Male	56	Right	No
3	Female	26	Right	No
4	Female	32	Left	No
5	Male	26	Left	No
6	Female	36	Left	No
7	Female	40	Right	No
8	Female	35	Left	No
9	Female	34	Left	Yes
10	Female	40	Right	Yes
11	Female	25	Left	Yes
12	Male	53	Left	Yes
13	Female	50	Right	Yes
14	Female	32	Left	Yes
15	Male	33	Left	Yes
16	Female	30	Right	Yes
17	Female	24	Left	Yes
18	Female	26	Left	Yes
19	Male	28	Left	Yes
20	Female	19	Right	Yes
21	Female	47	Left	Yes
22	Female	17	Left	Yes

quantitative neuropsychological evaluation. Electroencephalography and imaging interpretation was performed by a multidisciplinary team blinded to the network modeling parameters. This study was approved by the local institutional review board and all participants signed informed consent.

2.2. Data acquisition

Electroencephalography and rsfMRI were obtained on two separate visits and were therefore not concurrently acquired. Electroencephalography was acquired with 24 scalp electrodes in a standard International 10–20 configuration during the preoperative LTM session. rsfMRI was conducted in a 3-Tesla MRI with a blood oxygenation level-dependent (BOLD) MRI sequence. Resting state functional MRI was acquired with the patient lying supine with eyes closed. Volumetric T1-weighted thin slice MRI was acquired during the same session.

2.3. Network modeling

The epilepsy network for each patient was modeled as previously described [17]. Briefly, all MR image sets were motion corrected, smoothed, and transformed into Montreal Neurological Institute (MNI) space using the six-parameter rigid body spatial transformation algorithm and coregistered using SPM12 (Wellcome Department of Imaging Neuroscience, University College London, UK). The scalp EEG data were filtered to remove nonphysiologic frequencies and cropped to include only the interictal or ictal signals identified by a blinded neurophysiologist (MATLAB 2016b, Natick, MA). Ictal and interictal source discharges were localized by first generating a transformed mesh from the thin-slice T1-weighted MRI sequence. Then, cortical dipoles were modeled using a forward computation that was followed by empirical Bayesian approach to inverse reconstruction, localizing the theoretical evoked response (SPM12). This process was used to generate a hypothesized irritative zone source volume, which was coregistered to the rsfMRI in MNI space. The irritative zone may also be referred to as the hypothesized epileptogenic zone and is localized based on the first electronic signature of seizure activity measured on EEG. The rsfMRI time-series signature was extracted from the irritative zone volume, and intraaxial image voxels with an above-threshold Pearson correlation coefficient were compiled to create a set of volumes representing the putative epileptic resting network. The rsfMRI threshold was defined as the average Pearson correlation coefficient for each patient. We chose the average as a threshold to correct for potential variations in scan conditions and intrinsic connectivity differences between patients. These volumes were comprised of voxels with high degree of correlation with the irritative zone and were not based on any functional atlas or prior knowledge or presumption of existing networks. In this way, the network models were developed a priori, which is different from most studies in this area. Our network modeling algorithm has been detailed and validated in a prior study [17]. Additionally, patient #9 of this project was included in the prior study to demonstrate the novel network modeling algorithm. Network models were also acquired for six age-matched healthy control patients who had no history of seizures. The control group consisted of two females and four males, ranging in age from 23 to 42 years with a mean age of 29 years. Determination of seizure surgery and seizure lateralization and localization were made independent of the network models data.

2.4. Global connectivity

While the epilepsy network described above was a voxel-level analysis, a region of interest (ROI) level connectivity analysis was also conducted to add another perspective to the results. An atlas of ROIs generated in a prior study of rsfMRI datasets was applied to these patients to generate a more global analysis of connectivity in these patients [18]. The average time series for each ROI was used to generate a connectivity matrix of Pearson correlation values. The ROIs were split into groups based on the hemisphere. When there was a concordance of evidence that the seizure onset was in either the left or right temporal lobe based on video-EEG and semiology, it was deemed to be the ipsilateral hemisphere. In this cohort, 14 of 22 patients (64%) had a hypothesized left-sided seizure onset with the remainder presumed to be in the right temporal lobe, with cases of bitemporal onset excluded from the analysis. A matrix of edges was generated mathematically that represented each connection between two ROIs, and the corresponding Pearson correlation coefficient representing the relative connectivity between those two ROIs. The matrix of edge connections was used to generate an average connectivity for the whole brain by averaging the Pearson correlation coefficient for every single connection within the patient being analyzed. Connections were generated between 81 ROIs defined in a previous study from healthy patients' rsfMRI data to estimate the degree to which normal connectivity was affected in patients with epilepsy [18]. These 81 ROIs were predefined volumes that were overlaid on the patient images from this study to study the connectivity, and effectively acted as a resting-state functional atlas. Edges, aka connections, that had a Pearson connectivity coefficient greater than the average of the whole brain connectivity were determined to be “above average connections.” Above average connections were counted in each hemisphere as a metric for interconnectivity.

2.5. Healthy control network modeling

The images from the healthy control patients were preprocessed and transformed into MNI space in the same way as the images from the TLE cohort. The epileptic network maps created from the patients with TLE were then superimposed on the rsfMRI from each healthy control, and the connectivity matrix was calculated. Mean Pearson correlation coefficients were calculated to determine the functional connectivity of the epileptic network maps superimposed in healthy patients who were not supposed to have increased connectivity in the regions of the modeled epilepsy networks. This step was performed to confirm that the modeled epilepsy networks in the TLE cohort were more functionally connected than the control.

2.6. Neuropsychological testing

Both pre- and postoperatively, twelve patients completed comprehensive neuropsychological assessment following National Institutes of Health (NIH) Epilepsy common data elements recommendations that quantify aspects of cognition including declarative memory, attention/executive, language, and visuoconstructional functions as well as general intellectual ability. Subtests of the Wechsler Memory Scale-4th Ed. (WMS-IV) and Rey Auditory Verbal Learning Test (RAVLT) were used to measure verbal immediate memory (Logical Memory Immediate recall subtest [LM-I], RAVLT Trial 6) and verbal delayed memory (Logical Memory Delayed recall subtest [LM-II], RAVLT Trial 7) [19]. Visual immediate memory measure included the WMS-IV Visual Reproduction Immediate Recall (VR-I) subtest and visual delayed memory measures including WMS-IV Visual Reproduction Delayed Recall (VR-II) subtest and the Rey–Osterrieth complex figure test (ROCFT)-delay task. Visual immediate memory (VR-I) and visual delayed memory (VR-II, ROCFT-D) measures were measured. Letter and semantic verbal fluency tasks including the Controlled Oral Word Association Test (COWAT-FAS) and animal semantic fluency task was measured. Confrontation naming was measured using the Boston Naming Test (BNT). Executive measures including the Wisconsin Card Sorting Test and the Ruff Figural Fluency Test (RFFT) were measured. The RFFT provides a measure of nonverbal mental flexibility including unique designs (higher scores are better performance) and perseverative errors error ratio (higher scores are worse performance). Finally, each patient completed the Wechsler Adult Intelligence Scale-4th Ed (WAIS-IV) prorated full-scale intelligence index. Raw scores for all neuropsychological

tests except for WAIS-IV IQ scores were used in analyses. Descriptive statistics for this cohort are given in Table 2.

2.7. Statistical analysis

Neuropsychological data and the network metrics were compared using a Spearman Rho correlation coefficient analysis. All statistical tests were conducted using IBM SPSS Statistics Version 25 (IBM Corp., Armonk, New York, United States). No patients were excluded at any stage during the analysis. p-Values less than $\alpha = 0.05$ were considered significant.

3. Results

3.1. Demographics

For the cohort of 22 patients with TLE, the average age at the time of surgery was 33.6 ± 10.3 years with age ranging from 17 to 56 years old. Left-sided temporal lobe surgery was conducted on 14 of 22 (64%), with the remainder on the right side. Females comprised 16 of 22 (73%) patients. Duration of epilepsy was calculated as the time from first seizure to the time of surgery, which averaged 14.3 ± 10.3 (standard deviation [S.D.]) years and ranged from 1.4 to 22 years. Patients were followed for an average of 18.4 ± 4.9 months for seizure recurrence, with a minimum follow-up time of 8.4 months. As of the last follow-up, 15/22 (68%) patients were seizure-free (Engel Class I).

Table 2
Neuropsychological testing values.
Difference score = Post-op score − pre-op score.

Test name		Minimum	Maximum	Mean	Standard deviation
FSIQ	Pre-op score	64.0	112.0	89.0	14.4
	Post-op score	61.0	118.0	89.5	15.2
	Difference score	−18.0	16.0	1.5	8.5
LM-I	Pre-op score	8.0	39.0	22.4	9.6
	Post-op score	10.0	31.0	19.7	8.4
	Difference score	−19.0	6.0	−3.7	8.1
LM-II	Pre-op score	5.0	39.0	19.1	10.6
	Post-op score	8.0	29.0	18.5	7.9
	Difference score	−14.0	8.0	−1.8	6.6
VR-I	Pre-op score	21.0	43.0	33.6	7.1
	Post-op score	24.0	42.0	32.9	5.8
	Difference score	−14.0	7.0	−1.1	6.1
VR-II	Pre-op score	4.0	35.0	20.6	9.3
	Post-op score	5.0	41.0	21.0	13.0
	Difference score	−13.0	17.0	0.8	8.9
FAS	Pre-op score	5.0	43.0	27.3	10.1
	Post-op score	25.0	40.0	32.5	5.6
	Difference score	−4.0	22.0	5.6	8.3
Animal Naming	Pre-op score	5.0	27.0	16.5	6.5
	Post-op score	10.0	22.0	15.5	4.0
	Difference score	−13.0	7.0	−1.2	6.6
RAVLT-6	Pre-op score	0.0	15.0	8.2	5.1
	Post-op score	1.0	13.0	8.5	4.4
	Difference score	−5.0	7.0	0.2	3.7
RAVLT-7	Pre-op score	0.0	15.0	7.2	5.4
	Post-op score	0.0	14.0	8.4	4.5
	Difference score	−4.0	8.0	0.5	3.9
BNT	Pre-op score	31.0	57.0	47.8	8.7
	Post-op score	22.0	55.0	46.2	11.2
	Difference score	−22.0	8.0	−3.5	8.5
RFFT-UD	Pre-op score	35.0	55.7	42.8	7.4
	Post-op score	32.0	52.0	40.5	5.9
	Difference score	−15.0	24.0	−0.9	12.4
RFFT-ER	Pre-op score	37.0	73.0	58.4	12.6
	Post-op score	38.0	67.0	53.4	10.2
	Difference score	−0.8	0.1	−0.1	0.3

Abbreviation: RFFT-UD, Ruff figural fluency test - unique designs.

3.2. Preoperative global connectivity

Global network connectivity was measured using a functional 3D atlas determined from a collection of rsfMRI datasets from twenty-seven healthy patients [18]. Connectivity between atlas-based ROIs was computed using Pearson Product moment correlation, and average correlation values were calculated for the whole brain. Higher mean global connectivity correlated with worse scores in a preoperative neuropsychological measure of nonverbal executive functioning (RFFT-ER; $R = 0.943$, $p = 0.005$) and with worse Wada memory scores contralateral to seizure onset ($R = -0.0577$, $p = 0.015$). A higher proportion of above-average connections in the hemisphere contralateral to the hypothesized seizure onset correlated with impairment in executive functioning (RFFT-ER; $R = 0.943$, $p = 0.005$). Increased global connectivity within the contralateral hemisphere correlated with impairment in both short- and long-term measures of visual memory and learning (RAVLT6, RAVLT7 raw; $R = -0.650$, $p = 0.020$, $R = -0.676$, $p = 0.030$). Two examples are shown in Fig. 1 comparing a patient's global network that is more symmetric with above-average edges more evenly distributed between the two hemispheres with a patient whose global network is more asymmetric, with a larger number of above-average edges contralateral to the modeled irritative zone.

3.3. Epilepsy network connectivity

Epilepsy networks were modeled in each patient and represented connectivity related specifically to the hypothesized irritative zone based on video-EEG. Localization of the epilepsy network was determined by determining how many voxels of the epilepsy network that overlapped with the area of interest (i.e., ipsi- or contralateral hemisphere, bitemporal lobes) from a predefined atlas. Two example epilepsy networks are shown in Fig. 2, showing that the network spread can either be widespread or local with an irritative zone ROI in the same location. Localization of the epilepsy network in the bitemporal lobes was computed as a fraction of the total epilepsy network, and higher bitemporal lobe localization correlated with lower scores in verbal learning and short-term memory (RAVLT6; $R = -0.671$, $p = 0.024$). Relationship with verbal delayed memory measures was non-significant but similarly exhibited a large effect size (RAVLT7; $R = -0.566$, $p = 0.070$).

3.4. Correlation with outcomes

Patients were grouped into either “seizure-free” ($n = 15$) or “not seizure-free” ($n = 7$) based on their Engel Class outcome score. Seizure recurrence occurred in 35% of patients, consistent with previously published rates [20,21]. Based on the total sample ($n = 22$), higher rates of seizure recurrence correlated with localization of the epilepsy network to the bitemporal lobes ($R = -0.542$, $p = 0.014$), with a unique significant correlation found with localization to the contralateral temporal lobe ($R = -0.530$, $p = 0.016$).

4. Discussion

4.1. Main findings and impact

In the present study, we prospectively analyzed a cohort of 22 patients with TLE and found that certain patterns of resting state connectivity were correlated with neurocognitive dysfunction and outcomes. Both global and epilepsy-specific connectivity was found to be strongly associated with measures of neurocognitive functions. Increased connectivity contralateral to seizure onset was correlated with impaired objective measurements of executive functioning and verbal memory. In addition, epilepsy-related network spread located in the bitemporal lobes and, in particular, to the contralateral temporal lobe was

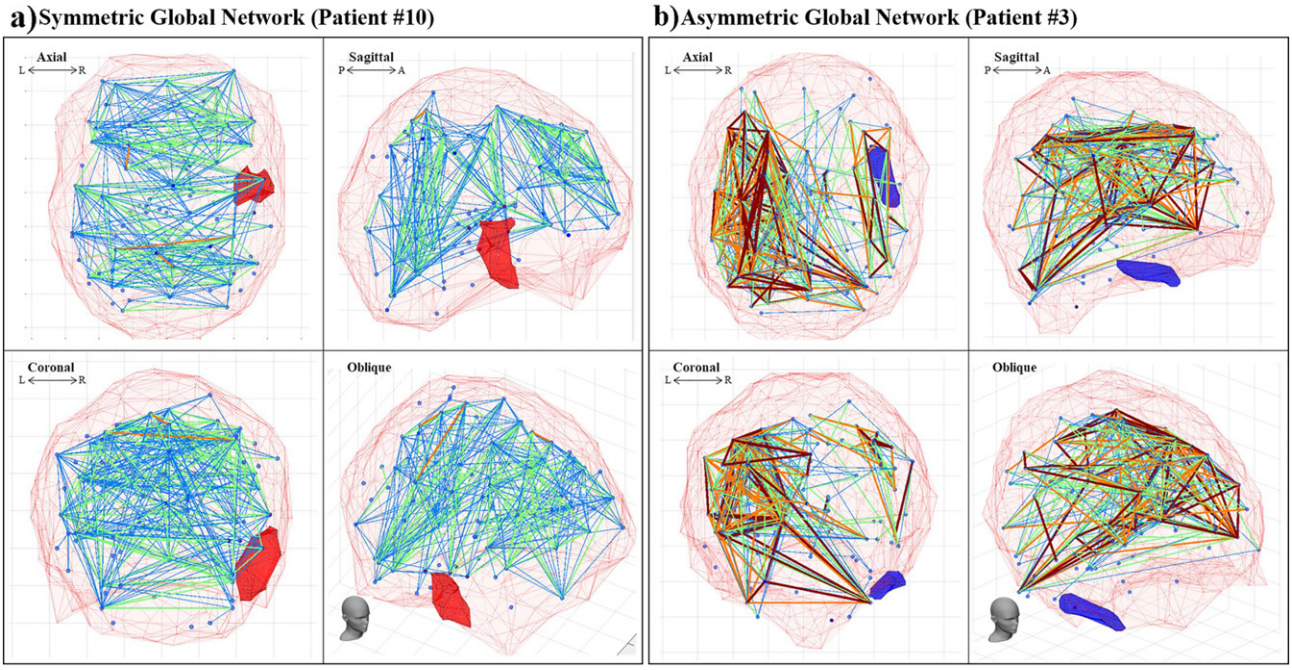

Fig. 1. Example 3D models are shown to compare two patients with different global network distributions. Axial, sagittal, coronal, and oblique projections of the 3D model are shown with blue dots representing the centroid of the functional ROIs used to measure the global connectivity. Lines connecting the blue dots represent edges, and the color of the line represents the Pearson correlation coefficient, with blue lines having relatively lower connectivity and dark red lines having the highest connectivity. The solid red or blue volume represents the hypothesized irritative zone generated from surface EEG as described in the Materials and methods section.

a) Patient #10 is shown as an example of a global network that is symmetrical. Edges are more evenly distributed between the two hemispheres. This patient was seizure-free after surgery.
b) The global network from Patient #3 is clearly more asymmetric by comparison, with more edges in the hemisphere contralateral to the irritative zone. This patient was not seizure-free after surgery.

associated with impaired verbal learning and short-term memory. Bitemporal lobe localization was also associated with higher rates of seizure recurrence.

Neurocognitive changes in TLE are classically associated with memory function impairment, including deficits in verbal memory as a result of hippocampal/mesial temporal damage from seizures [22,23]. Large

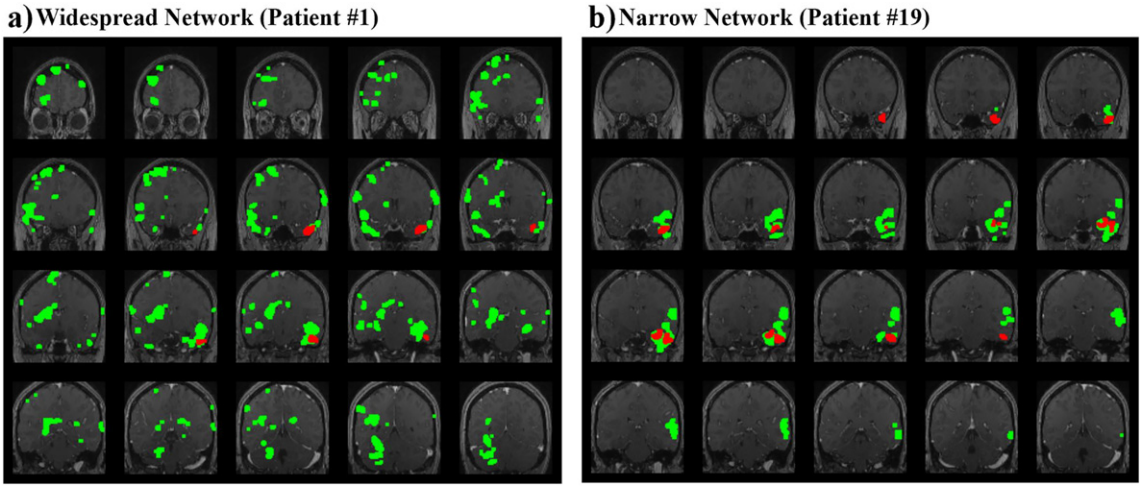

Fig. 2. Example coronal image sets are shown here to demonstrate the variability in epilepsy networks between patients. In these figures, the epilepsy network is shown, which is modeled separately from the global network. The irritative zone is shown in red, and the voxels in green are the brain regions that are highly correlated with the irritative zone. These green volumes represent the epilepsy network, which is further described in the Materials and methods section.

a) Patient #1 is shown as an example of an epilepsy network that is widespread; it is distributed through both hemispheres and bitemporal lobes. This patient was not seizure-free after surgery.
b) The global network from Patient #19 is much more localized in comparison, with no involvement of the contralateral hemisphere. The connected cortex in this narrow network is localized very near to the irritative zone. This patient was seizure-free after surgery.

correlations were shown between network connectivity outside the irritative temporal lobe and measures of executive functions and verbal learning/short-term memory that suggests extensive network alterations in TLE visualized with rsfMRI. Functional outcomes related to extratemporal involvement of seizures or seizure networks has been observed, but few functional MRI studies have demonstrated a correlation between degree of dysfunction in specific neuropsychological domains and rsfMRI connectivity patterns [24,25]. In particular, to our knowledge, no one has mapped extratemporal networks and related them to objective neuropsychological measures of frontal lobe function.

These data support observation by Hermann et al. that reported that MRI structural abnormalities were observed to extend well beyond the ipsilateral temporal lobe among patient's exhibiting more cognitive deficits [26]. These findings extend Chang, Marshall et al.'s findings of increasing neurocognitive deficits with structural white matter abnormalities involving the entire frontal and temporolimbic regions ipsilateral to the seizure region, which were strong predictors of verbal memory [27]. Chang et al. found that rsfMRI abnormalities in the left mesial temporal lobe were particularly predictive of verbal memory deficits in patients with left MTS, but also observed among patients with left TLE. Similar to Chang et al., we observed a particularly strong relationship between rsfMRI of the left mesial temporal/posterior cingulate cortex for a score of verbal list learning (California Verbal Learning Test (CVLT) list learning). However, Chang et al. did not evaluate the epilepsy network itself, and the results were limited to the global connectivity network.

A better understanding of how functional imaging relates to cognition is important in TLE because it could guide the decision on whether the patient will elect for surgery or medical management. Before surgery, an rsfMRI could be obtained to determine if a patient has contralateral connectivity disturbances, which would suggest more widespread involvement of the seizure networks. Widespread involvement may be more difficult to treat because there is no focus of impaired activity that can be modulated or resected, and there has been a significant amount of work demonstrating the utility of rsfMRI in predicting seizure outcomes after surgery [28]. Prior studies have identified that certain network disturbances correlated with refractoriness to surgery, so there is a growing body of knowledge that supports the use of rsfMRI in the preoperative workup for TLE [29].

4.2. Future studies

Widespread networks were shown to impair cognitive function, but a more granular understanding of how network spread affects cognition and seizure outcomes is not well understood. In future studies, we hope to expand the existing literature on network hubs by identifying particular regions of the epilepsy network that may be most involved with functional impairment, or which areas are most likely to impede epileptogenesis if resected or modulated. Further identification of network parameters that predict patient outcomes and functional impairment may aid in patient selection, resection planning, and ultimately the efficacy of epilepsy surgery.

4.3. Limitations

While not detracting from the results of this study, there are some limitations with our methods that should be addressed. Our sample size of 22 patients is still relatively small, but this is a pilot study of a relatively homogenous patient population. With these results, we hope to stimulate further research in the field of network neuroscience in TLE and expand upon these results as we add more patients. Furthermore, this study was conducted using surface EEG, which is notoriously deficient at detecting seizure foci in the frontal lobe. Although the semiology and EEG signature of these patients was consistent with temporal lobe onset, we cannot rule out the possibility that some of these patients had focal onset in the frontal lobe that might have contributed to the measured frontal lobe dysfunction. We hope to supplement these data with invasive monitoring in future patients, which may address this shortcoming.

5. Conclusion

Using a noninvasive automated network modeling software algorithm, we obtained preoperative rsfMRI for 22 patients with TLE. Aberrant connectivity patterns related to epileptogenesis and atlas-based ROIs in the hemisphere contralateral to epileptogenesis was correlated with impairment in executive functioning and learning. Spread of the epilepsy network to the bitemporal lobes was associated with seizure recurrence. Widespread extratemporal involvement of seizure networks may be related to the executive functioning deficiencies that have long been associated with TLE syndromes.

Declaration of competing interest

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

Acknowledgments

None.

Author statement

All authors affirm that the work described is consistent with the guidelines for ethical publications of *Epilepsy and Behavior*. All authors made significant contribution to the study and preparation of the manuscript and have approved the final version for submission and accept responsibility for its content. No undisclosed groups or persons have had a primary role in the study or manuscript preparation.

Ethical publication statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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