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Surgical disconnection of epilepsy network correlates with improved outcomes

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ABSTRACT

Purpose: A novel software algorithm combining non-invasive EEG and resting state functional MRI data to map networks of cortex correlated to epileptogenic tissue was used to map an epilepsy network non-invasively. The relationship between epilepsy network connectivity and outcomes after surgery was investigated using this non-invasive and non-concurrent modeling algorithm.
Method: Scalp EEG and resting state functional MRI were acquired for nineteen patients with temporal lobe epilepsy. The hypothetical irritative zone was mapped, and resting state functional MRI data was used to model regions functionally correlated with the irritative zone. Epilepsy network connectivity was measured in patient with temporal lobe epilepsy ($n = 19$) both pre- and post-operatively. Temporal networks were also mapped in healthy control participants ($n = 6$).
Results: Thirteen of nineteen patients (68 %) were seizure free after 20.3 ± 4.8 months. Epilepsy network connectivity within the temporal lobe was significantly higher among patients with temporal lobe epilepsy compared to the healthy control patients ($p < 0.05$). Disconnection of the epilepsy network was significantly higher in patients who were seizure free. Using spearman rho analyses, neuropsychological function after surgery was found to be relatively better in patients with higher degree of epilepsy network disconnection.
Conclusions: The magnitude of network disconnection after surgery was strongly associated with increased rates of seizure freedom and relatively better neuropsychological measures of memory and naming function. It was shown that seizure-free outcomes and relatively improved neuropsychological function correlated with surgical disconnection of a highly synchronous epilepsy network.

1. Introduction

1.1. The need for a network algorithm

For the 20–30 % of patients with temporal lobe epilepsy (TLE) refractory to medical therapy, resective brain surgery is an effective option that results in seizure freedom in approximately two-thirds of cases [1]. Surgical disconnection of the epileptogenic tissue is the goal of each type of epilepsy surgery, and in TLE this typically occurs with resection of the hippocampus, amygdala, and/or the anterior temporal lobe [2]. Development of technology that allows for more accurate and precise surgical target mapping or better identification of ideal surgical candidates may lead to a higher rate of seizure-freedom in patients with TLE undergoing surgery. Current planning methods involve a two-stage surgery with implanted electrodes that localize seizure foci over the course of a few days and then a follow-up surgery where foci are resected. While this method is effective, a non-invasive method to plan resections would be more desirable because there is less risk to the patient.

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; FSIQWechsler Adult Intelligence Scale-4th Ed., Full Scale Intelligence Quotient; LM-IWechsler Memory Scale-4th Ed., Logical Memory Immediate recall subtest; LM-IIWechsler Memory Scale-4th Ed., Logical Memory Delayed recall subtest; VR-IWechsler Memory Scale-4th Ed., Visual Reproduction Immediate Recall subtest; VR-IIWechsler Memory Scale-4th Ed., Visual Reproduction Delayed Recall subtest

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Table 1
Demographics.

A. Seizure-Free					
Patient	Sex	Age at Surgery (years)	Surgery Side	MRI/Pathology	(^{18}F-FDG) PET
1	Female	33	Left	MTS	Left temporal hypometabolism
2	Male	25	Left	MTS	Left temporal hypometabolism
3	Male	32	Left	Negative	Left temporal hypometabolism
4	Female	40	Right	MTS	Right temporal hypometabolism
5	Female	53	Left	MTS	Negative
6	Female	30	Right	Negative	Right temporal hypometabolism
7	Female	34	Left	MTS	Left temporal hypometabolism
8	Female	47	Left	MTS	Left temporal hypometabolism
9	Female	19	Right	MTS	Right temporal hypometabolism
10	Male	26	Left	MTS	Left temporal hypometabolism
11	Male	17	Left	Negative	Left temporal hypometabolism
12	Female	28	Left	MTS	Left temporal hypometabolism
13	Female	24	Left	Negative	Negative
B. Not Seizure-Free					
Patient	Sex	Age at Surgery (years)	Surgery Side	MRI/Pathology	(^{18}F-FDG) PET
14	Male	26	Left	Left MTS	Left temporal hypometabolism
15	Female	27	Right	Negative	Right temporal hypometabolism
16	Female	32	Left	Negative	Left temporal hypometabolism
17	Female	40	Right	Negative	Right temporal hypometabolism
18	Female	34	Left	Negative	Left temporal hypometabolism
19	Female	35	Left	Negative	Bitemporal hypometabolism

1.2. Brain networks in epilepsy

The expanding field of brain network analysis has revealed irregularities in the brains of patients with TLE outside the hypothesized irritative zone include decreased global connectivity, decreased connection to the default-mode network, and isolation of networked cortex in the region of the irritative zone [3–5]. Analysis of networks is conducted using resting state functional MRI (rsfMRI) and electroencephalography (EEG) because these methods allow for measurement of brain activity with high spatial and temporal resolution [6–8]. Recently, we published a novel network modeling algorithm was developed that uses only non-invasive and non-concurrently acquired data from patients with epilepsy to map an epilepsy network, a technique that will be further analyzed in the present study, and found that widespread networks were correlated with impaired executive and verbal memory function [9,10]. The reported and hypothesized utility of network modeling in epilepsy ranges from irritative zone identification, cognitive performance assessment, and prediction of surgical outcomes [11]. While previous studies have focused and atlas-based segmentation and hypothesized networks, our model was formed without a specific network constraint so we could better automate the processing. Automatic processing allows for less bias and inter-rater variability because there are fewer choices that the user has to make that influence the final network map.

1.3. Neuropsychological changes with epilepsy and after epilepsy surgery

Individuals with medication refractory epilepsy are at risk of neuropsychological decline, including memory, language, visuoconstructional and attention/executive functions without undergoing surgery, with 20–25 % showing a reliable decline after four years [12]. Post-surgical changes in cognitive function in patients with epilepsy are heterogeneous, depending on the pre-operative level of function, age, and surgical approach, but commonly involve declarative memory, language, executive, and visuoconstructional functions [13]. A meta-analysis found the largest decline post-operatively in memory and language, aspects of attention/executive and visuoconstructional functions [14]. The greatest risk for neuropsychological decline is typically associated with language dominant temporal resections involving aspects of language and verbal memory [15,16]. It is hypothesized that interruption of normal networks and changes in brain structure both ipsilateral and contralateral to the seizure focus contributes to this decline, and suggests that prompt definitive treatment may slow or halt the decline [17]. In addition to adverse neuropsychological effects of epilepsy and surgical treatment for epilepsy, quality of life is negatively affected by epilepsy, and is generally improved with seizure freedom [18,19]. Neuropsychological evaluation of each patient is important to avoid the negative impacts of surgery and maximize the benefits from early intervention.

1.4. Surgical outcomes related to network parameters

Network hub resection, pre-operative network ictogenicity, and characteristic “epileptic” connectivity patterns have been shown to offer prognostic value as a biomarker in predicting response to epilepsy surgery [11,20–24]. These findings emphasize the growing need for epilepsy care teams outside major academic institutions to consider the adoption of network analysis into their practice. However, the state-of-the-art network modeling assays are reliant on invasive electrocorticography (ECoG) or concurrently acquired rsfMRI/EEG data. Invasive monitoring confers risk of surgical complications to the patient, and concurrent rsfMRI/EEG acquisition assays are likely out of the reach of many clinical centers due to the need for long MRI acquisition times and specialized MRI-compatible scalp EEG. A non-invasive and non-concurrent method of modeling networks would be a reasonable alternative if it could measure network properties with reasonable specificity and sensitivity.

1.5. Objective

Using a network modeling algorithm built from non-invasive and non-concurrent data, we investigated the relationship between epilepsy network connectivity and surgical outcomes including seizure freedom and cognition.

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 and was approved by our university's Institutional Review Board (IRB). Epileptic networks were modeled in nineteen patients with unilateral TLE, characterized by focal temporal lobe seizures. Each patient was selected for surgery based on presence of temporal lobe semiology and congruent findings in EEG and MRI as listed in Table 1. The surgical technique was classified as either a selective transcortical amygdalohippocampectomy (SAH), or a transcortical amygdalectomy with minimal resection of the hippocampus to spare memory function. One patient (Patient #19) also had invasive electrodes implantation (phase 2 monitoring) for further localization of seizures. The invasive monitoring data was not used in the network analysis. The patients included in this study represent a consecutive series of nineteen patients with TLE who signed consent and agree to participate in this study. They underwent this pre-operative network assessment and surgery at our tertiary referral center (Table 1). Each patient underwent a standard pre-surgical evaluation for epilepsy surgery including MRI, long-term EEG monitoring (LTM), Wada testing, ^{18}Fluoro-2-deoxyglucose positron emission tomography ((^{18}F-FDG) PET), and neuropsychological testing. Surgery planning and post-surgical evaluation not related to network analysis were conducted by a care team blinded to the epileptic network modeling results. Additionally, rsfMRI images were 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 with a mean age of 29 years.

2.2. Data acquisition

EEG and rsfMRI were obtained on two separate hospital visits as part of a standard pre-surgical evaluation. EEG was acquired with 24 scalp electrodes in a standard International 10–20 configuration during the pre-operative LTM session. rsfMRI was conducted in a 3-Tesla MRI with a blood oxygenation level dependent (BOLD) MRI sequence. rsfMRI was acquired with the patient lying supine with eyes closed. The rsfMRI sequence consisted of a single five-minute acquisition with parameters as follows: echo time (TE) of 35 ms, repetition time (TR) of 3000 ms, and a voxel size of 4 × 3.75 × 3.75 mm. Volumetric T1-weighted thin slice MRI was acquired during the same session. The post-operative MRI was conducted four months after the surgery to allow the acute surgery-related MRI signal to dissipate and not affect our results.

2.3. Network modeling

The epilepsy network for each patient was modeled as previously described [9]. A visualization of the methodology is also shown in Fig. 1. 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 co-registered using SPM12 (Wellcome Department of Imaging Neuroscience, University College London, UK). The scalp EEG data were filtered to remove non-physiologic frequencies and cropped to include only the inter-ictal or ictal signals identified by a blinded neurophysiologist (MATLAB 2016b, Natick, MA). Ictal and inter-ictal 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 an 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 co-registered to the rsfMRI in MNI space. Representative images showing the result of the inverse localization for each patient are shown in Supplementary Fig. 1. The rsfMRI time-series signature was extracted from the irritative zone volume and intra-axial image voxels with an above-threshold Pearson correlation coefficient were compiled to create a set of volumes representing the putative epileptic resting network. This network consisted of cortical regions separate from the irritative zone, and connectivity within the network was computed by averaging the Pearson correlation coefficients between voxels within the network. In other words, the epilepsy network was mapped and then connectivity was determined within that network using an average of the Pearson correlation coefficients. Post-operative connectivity within the modeled network was determined by calculating the mean Pearson connectivity coefficient within the network using the post-operative rsfMRI image set. Average connectivity values were compared between pre and post-operation scans and used to compute a "percent disconnection." Percent disconnection represented the percentage decreases in connectivity after surgery, and was calculated by the formula: 100 x (1 – post/pre), where "post" is the post-operative connectivity and "pre" is the pre-op. This analysis was in no way derivative of previous segmentations or functional atlas determined in previous studies. The network was mapped without prior knowledge of any parameters in the rsfMRI for each patient. An example of the epilepsy network map from one patient is shown in Fig. 2. Of note, patient #7 was included in the prior study to demonstrate the novel network modeling algorithm [9].

2.4. Healthy control network modeling

The images from the healthy control patients were pre-processed and transformed into MNI space in the same way as the images from the TLE cohort. The epileptic network maps created from the TLE patients 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

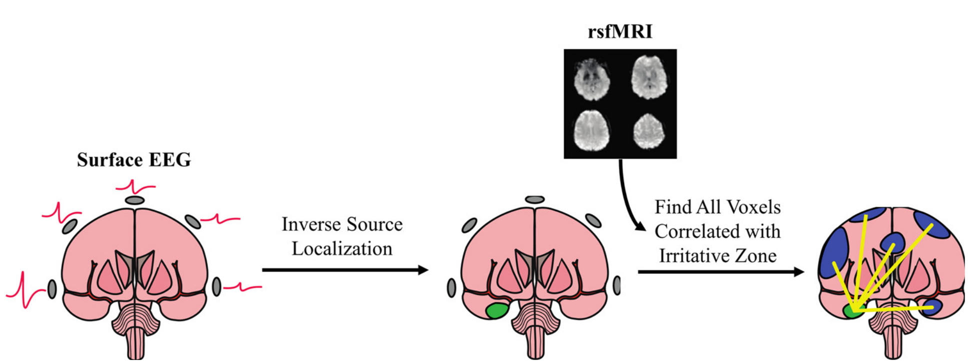

Fig. 1. Epilepsy network mapping methodology is shown in this figure. First, surface EEG is acquired and used to generate an estimated irritative zone (green) using inverse source localization techniques described in the materials and methods. Then, the irritative zone is localized with a non-concurrently acquired rsfMRI image set. The rsfMRI time series from within the irritative zone is correlated with every other voxel and voxels with Pearson correlation values above the threshold are included in the "epilepsy network" (blue).

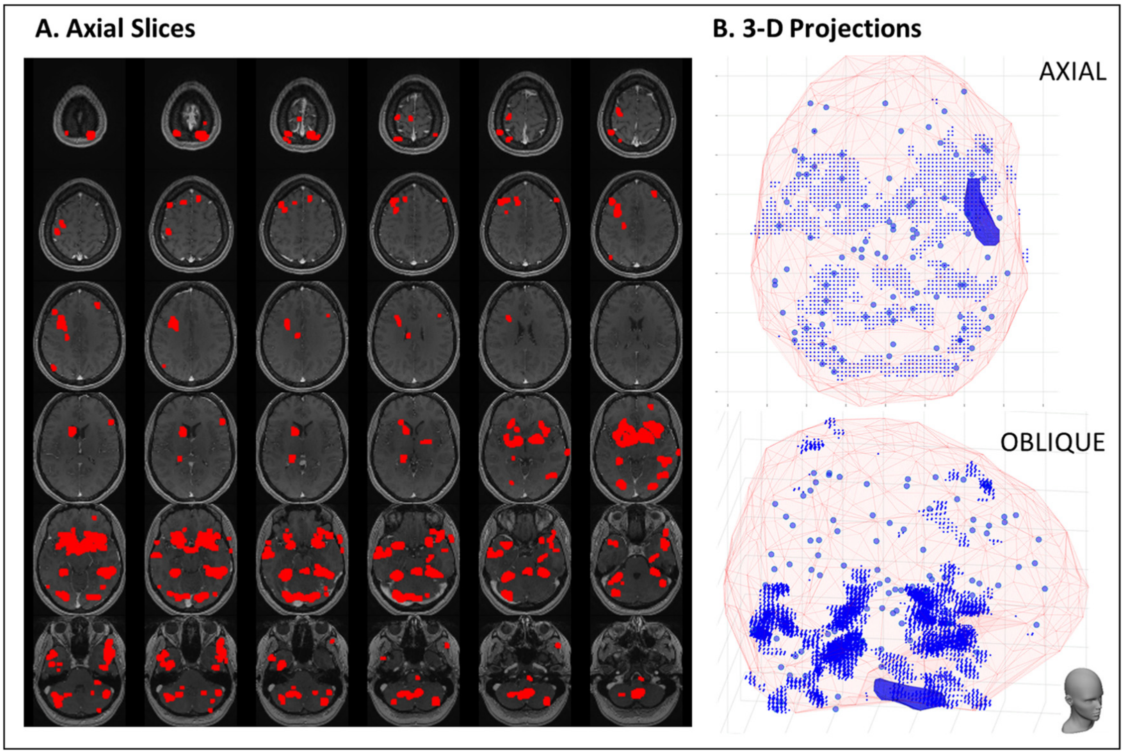

Fig. 2. Visualization of an example epilepsy network map from our modeling algorithm. This example is not meant to show specific aspects of the network, just to show a visual representation of the network spread from one patient.
A. A series of axial images from an example patient (#17 on Table 1) with the epilepsy network overlaid in red.
B. The model from the same patient is shown as a 3-D projection, with the putative irritative zone is shown in solid blue and the epilepsy network shown as a cloud of blue points.

functionally connected than the control.

2.5. Neuropsychological assessment

Both pre- and post-operatively, eight patients completed comprehensive neuropsychological assessment following 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. Quality of life and mood status was also obtained. Pre- and post-operative data were available for a subset of patients (n = 9) because data from the remaining patients are still being collected and processed. Testing and scoring were conducted by clinicians blinded to the network modeling results. Subtests of the Wechsler Memory Scale-4th Ed. (WMS-IV) analyzed immediate or delayed logical memory (LM-I & LM-II) and immediate or delayed visual reproduction (VR-I & VR-II), a measure of visual memory. The Rey Auditory Verbal Learning Test short-delay (RAVLT Trials 6) and long-delay (RAVLT 7) was used to measure auditory-verbal memory, rate of learning, learning strategies, retroactive and proactive interference, the presence of confabulation of confusion in memory processes, retention of information, and differences between learning and retrieval. Both RAVLT 6 & 7 and LM-I & II are tests that measure verbal memory. Verbal fluency was measured using the Controlled Oral Word Association (FAS) and semantic fluency was measured using the Animal Naming Test. Word retrieval was measured using the Boston Naming Test (BNT). The Ruff Figural Fluency Test (RFFT) evaluated nonverbal mental flexibility, initiation, planning, and divergent reasoning. 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.

2.6. Statistical analysis

A two-sample *t*-test was used to compare independent groups with continuous variables. *P*-values less than $\alpha = 0.05$ were considered significant. Network modeling statistical tests were conducted using GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). All neuropsychological data and the network metrics were compared using a Spearman Rho correlation coefficients and receiver operating characteristics (ROC) curve analyses for network disconnection variables were completed with IBM SPSS Statistics Version 24 (IBM Corp., Armonk, New York, United States).

2.7. Data availability

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

3. Results

3.1. Epileptic networks are unique to patients with TLE

Each patient's unique epileptic network was modeled using the algorithm described in the methods and in a prior publication from Neal et al. 2017 and then superimposed on images from the control group to compare connectivity. Epilepsy networks were developed using video-EEG analysis using 10–20 electrode placement. Suspected areas of seizure onset based on video-EEG were then mapped on MRI structural scans for regions of interest (ROI) where functional quantitative correlation analyses were completed among all areas of interest. When the epilepsy networks were overlaid on healthy control patients to determine a baseline connectivity matrix for reference, connectivity within the epileptic network for the TLE cohort was significantly higher

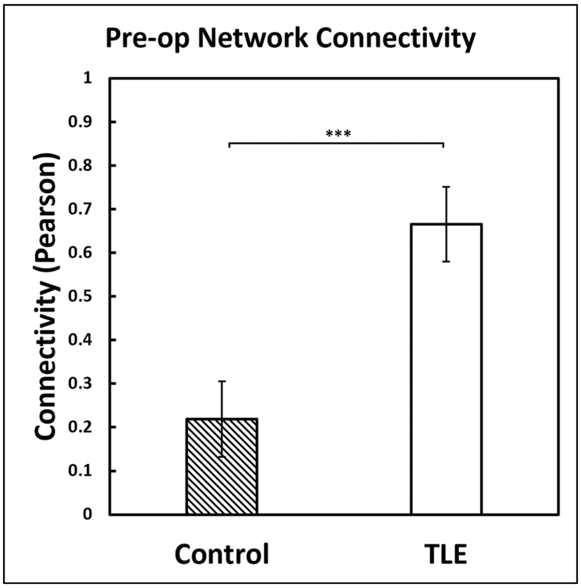

Fig. 3. Epileptic networks modeled in the patients with TLE were superimposed on images from healthy control patients, and inter-network connectivity (Pearson correlation coefficient) was compared. In the TLE cohort, epileptic networks showed significantly increased connectivity compared to the connectivity of that same network superimposed in the healthy control patients. (N.S. – Not Significant) (statistical significance by paired *t*-test: * p < 0.05, ** p < 0.01, *** p < 0.001).

compared to connectivity in the healthy control group ($p < 0.05$). Network connectivity in healthy patients was not significantly different between network maps modeled in the patients with TLE (Fig. 3).

3.2. Network disruption correlated with seizure-freedom

At an average follow-up time of 20.3 ± 4.8 months post-surgery, thirteen patients were seizure free and six patients had at least one clinical seizure (not seizure free). For each individual patient, the epilepsy network model that was generated pre-operatively was co-registered to the post-operative images and inter-network connectivity was measured (Fig. 4). Percent disconnection is a calculation indicating the percent change in connectivity in the epilepsy network, where higher numbers indicate a greater disconnection (100 – post-op connectivity/pre-op connectivity). Percent disconnection was significantly ($p < 0.05$) higher in patients who were seizure free after surgery compared to those who were not (Fig. 5A). Also, when comparing just the post-operative connectivity between seizure-free patients and non-seizure free patients, epilepsy network connectivity was significantly lower in the seizure-free group ($p < 0.05$) (Fig. 5B). ROC curve analysis revealed that patients with percent disconnection greater than 50.5 % predicted seizure freedom with 67 % specificity and 75 % sensitivity (area under curve = 0.806) (Fig. 5C).

The presence of MTS (tissue specimen) was not correlated with the connectivity changes seen in the epilepsy network. Ten patients had MTS and nine patients did not, and 9/10 (90 %) of the patients with MTS were seizure free after surgery while 4/9 (44 %) of the patients without MTS were seizure free after surgery. Despite the fact that seizure freedom correlated with epilepsy network disconnection, the presence of MTS did not correlate with pre-operative epilepsy network connectivity (p = 0.8031), post-operative epilepsy network connectivity (p = 0.9148), or percent disconnection of the epilepsy network (p = 0.9981).

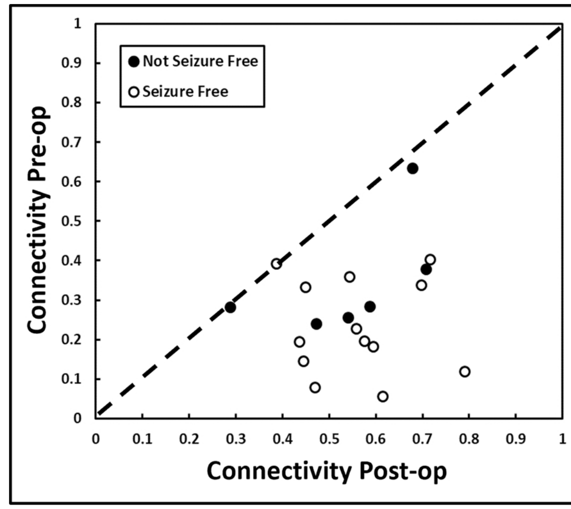

Fig. 4. Epileptic network connectivity is shown for each individual patient comparing the pre-operative and post-operative connectivity (Pearson correlation coefficient). The dashed line represents the point where pre-op and post-op connectivity are equal. Patients who were seizure free after surgery are represented with open circles, and patients who were not seizure-free are represented with closed circles.

3.3. Network disruption correlated with neuropsychological function after surgery

Several quantitative neuropsychological tests were conducted on patients both pre- and post-operatively. Mean pre-operative and post-operative scores for the TLE cohort are recorded in Supplementary Table 1. Nine patients had completed neuropsychological testing at this time, and 6 of 9 (67 %) were seizure free. Pre-operative scores were subtracted from post-operative scores (post-pre) to yield a “difference score,” where a higher positive score indicates improvement in post-operative function compared to the pre-op score. Difference scores were compared to the "percent disconnection" for each patient using the Spearman Rho correlation (Table 2). A positive correlation indicates that greater disconnection of the epilepsy network was associated with improved neuropsychological function. Correlation values closer to positive one indicates that epilepsy network disconnection was strongly associated with better outcomes in neuropsychological scores after surgery. Correlations approaching zero indicate that there was no relationship between the disconnection of the epilepsy network and neuropsychological test scores.

The BNT difference score (post-pre) significantly correlated with percent disconnection with a large effect (r_s = 0.676, $p < 0.05$). Difference scores from both verbal immediate and delayed semantic memory, LM-I (r_s = 0.718, $p < 0.05$) and LM-II (r_s = 0.497) respectively, exhibited a strong correlation with percent disconnection, but LM-II was not significant. Similarly, a measure of visual immediate memory, VR-I difference score strongly correlated (r_s = 0.442) with percent disconnection but was also not significant. Difference scores assessing IQ, verbal fluency, nonverbal mental flexibility (Ruff Figural Fluency Test), and another measure of verbal memory (Rey Auditory Verbal Learning) was not strongly correlated with percent epilepsy network disconnection.

4. Discussion

4.1. Network disconnection correlates with positive outcomes

In this study, a unique, highly connected functional network was mapped in patients with TLE. Each epilepsy network model was patient-specific, and connectivity within the voxels generated using the

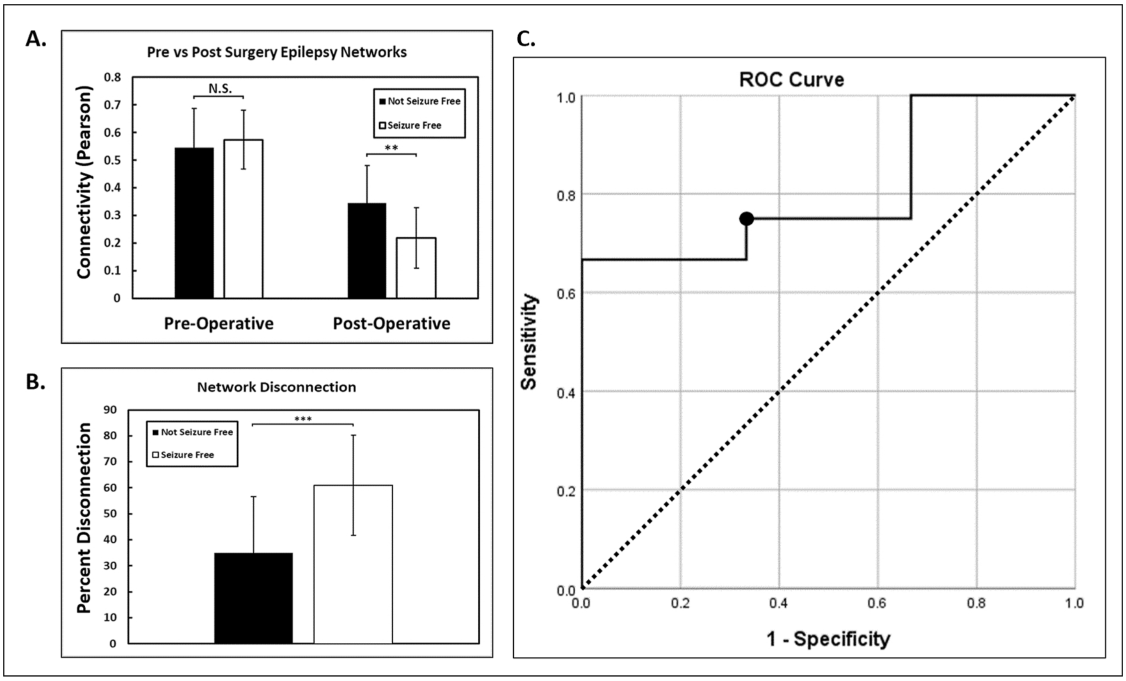

Fig. 5. A Pre-operatively, epileptic network connectivity in the seizure free and the non-seizure free cohorts was not significantly different. Additionally, epilepsy network connectivity in the seizure-free group was significantly lower than the non-seizure free group after surgery. (statistical significance by paired *t*-test: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

B. Percent disconnection of the epilepsy network was calculated by the formula: 1 – (post-op connectivity / pre-op connectivity). Percent disconnection in patients who were seizure free was compared to those who were not. It was found that seizure-free patients had a significantly greater percent disconnection than patients who did not ($p < 0.05$).

C. ROC curve analysis revealed that patients with percent disconnection greater than 50.5 % predicted seizure freedom with 67 % specificity and 75 % sensitivity (red marker). The area under the curve was 0.806, which a 95 % confidence interval with upper bound of 1.00 and lower bound of 0.600.

Table 2
Correlation Between Percent Disconnection and Neuropsychological Test Raw Scores (N = 9).

Test Name	Correlation Coefficient	p-value
LM-I Difference Score	0.718	0.030
BNT Difference Score	0.676	0.046
LM-II Difference Score	0.479	0.192
VR-I Difference Score	0.442	0.234
RAVLT6 Difference Score	0.386	0.386
RAVLT7 Difference Score	0.350	0.356
VR-II Difference Score	0.151	0.698
Animal Naming Difference Score	0.051	0.895
FAS Difference Score	−0.212	0.583
RFFT ER Difference Score	−0.264	0.568
RFFT UD Difference Score	−0.294	0.522

network modeling network was shown to be significantly higher in the TLE patients compared to healthy controls. It was shown that a higher degree of surgical disconnection of this network was strongly associated with patient's being seizure free at the time of follow-up. Furthermore, network disconnection was also correlated with a relative increase in neuropsychological functions related to verbal memory, visual memory, and language naming when evaluated with respect to seizure freedom, which are functions at least partially localized in the temporal lobe. There was the inverse relationship observed with a measure of non-verbal mental flexibility generally associated with frontal networks in which greater network disconnection was associated with relative decline in performance on this neuropsychological test.

4.2. Deleterious impact of the epilepsy network

Seizure propagation networks have been previously evaluated, but there has not been a specific network proposed that underlies the pathogenesis of epilepsy [25,26]. In the present study, it was shown that the network modeled using our previously published technique is involved in seizure generation and propagation. These data reinforce the importance of sufficient network disconnection in order to alleviate seizure burden and suggest that more disconnection also can positively impact neuropsychological functions that have been previously established to involve temporal lobe regions in patients with TLE. Evidently, disconnection of the epilepsy network is difficult to accomplish without disconnection of specific temporal lobe networks related to memory and naming, as suggested by the neuropsychological test scores showing a relative decrease in performance at post-op for the group. However, this relationship appears to not be linear and likely reflects the overlap of an epilepsy network and functional cognitive neuronetworks normally involved in cognitive functions. It is possible the current difficulty in predicting post-surgical neuropsychological and seizure freedom outcomes reflect patient-level differences between the epilepsy network and functional neuroanatomical networks that include temporal regions and/or those regions connected to the temporal lobe. The patient-specific differences between an epilepsy network and neuropsychological functions may also explain the variable degree to which some patients show improvement in some neuropsychological functions after becoming seizure free as well as how patients have seizure recurrence.

The lack of a strong correlation between the verbal learning test, the RAVLT, and percent disconnection was unexpected given these tests previously established sensitivity to the integrity of the language dominant Papez circuit [27]. However, review of Supplementary Table 1 reveals in this carefully selected group of patients with TLE, there was little change in RAVLT scores with the mean post-operative score being slightly improved from pre-operative scores. The limited sample size also prohibited analyses based on lateralization of seizure

surgery to language dominant hemisphere.

4.3. Utility of individualized network planning in surgery

These data suggest the possibility that seizures reinforce aberrant functional synchronicity, which is an "epilepsy network" involving neuroanatomical structures that interacts with cognitive functional networks to various degrees. There could be an inhibitory property of the epilepsy network that impairs certain neuropsychological functions, which would explain why those functions are relatively better after surgery in patients with more disconnection of the epilepsy network. Removal of the aberrant epilepsy network connectivity may become a goal of surgery to reduce seizure burden and potentially improve cognitive function. Similar to the finding of unique patient epilepsy network, it is likely the functional neuroanatomical networks for cognitive functions are patient specific and disrupted to various degrees by the epilepsy network in a dynamic manner. This interactive overlap of anatomic networks is also likely to be affected by duration of epilepsy with longer duration leading to greater disruption of functional neuroanatomical cognitive networks, strengthening and broadening the epilepsy network, and reducing the likelihood of seizure freedom or neuropsychological improvement following surgical treatment.

However, it is still unclear why some patients had more disconnection in the epilepsy network than others despite substantially similar surgical approaches. These data suggest that it is the inter-patient variability in the epilepsy network reflecting an aberrant pattern of synchronicity could explain why some patients fail to be seizure free despite similar pre-operative work-up findings using current Phase I and II technologies. It may be that network spread patterns underly the degree to which a temporal lobe surgery will sufficiently disrupt networks. It is possible that some patients' networks would have interconnectivty that is not routed through the temporal lobe and therefore would not be disconnected by temporal lobe surgery, and may require more extensive interventions (Fig. 6). The evaluation of the epilepsy network of each patient may provide an important variable to consider for patients with pharmacoresistant epilepsy and the degree to which the epilepsy network impairs a patient's functional neuroanatomic network for various cognitive functions (memory, naming). Pre-operative epilepsy network mapping could provide the needed individualized variable to improve our ability to predict post-operative outcomes and adapt surgical plans to improve efficacy [13–16].

The method to disconnect this epilepsy network can vary and the 'best' method remain to be determined, these data suggest that greater network disconnection was associated with higher rates of patient's being seizure free and better cognitive outcomes. These pilot data are particularly compelling because they suggest the possibility of targeting surgical disconnection of a patient-specific network to more effectively treat pharmacoresistant complex partial seizures. In an era of personalized medicine, patient-specific modeling and targeted surgery are becoming increasingly attractive because they may improve outcomes and decrease side effects. Further analysis of morphometric properties of the network model may help predict long-term outcomes after surgery and may facilitate early re-intervention if necessary.

4.4. Implementation of the modelling algorithm

This study shows that our network modeling algorithm using only non-invasive and non-concurrent data acquisition is sensitive enough to detect clinically relevant properties of functional networks in patients with TLE. The non-invasive nature of this algorithm will allow a treatment team to more safely monitor pathologic neural networks in the patient before and after surgery compared to invasive methods. The non-concurrent nature of the data collection simplifies the data acquisition because it does not require the purchase of specialized software for concurrent EEG and MRI acquisition. These two properties of this network algorithm are important for allowing widespread adoption of network modeling in any epilepsy center with EEG and MRI.

4.5. Future studies

In future studies, we aim to study which cortical or subcortical areas need to be resected in order to maximally disconnect the network. We will retrospectively study the resection cavity and its relationship to disconnection of the epilepsy network. With a better understanding of how exactly the network is disconnected, it may one day be possible that specifically targeting this epilepsy network in surgery will result in a higher proportion of patient's having successful resective surgery with seizure freedom rates that exceed current best reported rates of 66 % seizure free after five years [28]. Also, we will keep following the current cohort of patients, as seizure recurrence after a seizure-free period may depend on some aspect of the network parameters or its degree of disconnection.

4.6. Limitations

The data presented are preliminary, and as such, larger samples with longer duration of follow-up is needed to monitor for seizure recurrence and confirm the results of these pilot data. Time to follow up in this series is longer than a year, but seizure recurrence is known to occur in approximately 2 % of patients over four years after a seizure-free period following surgery, although recurrence in under six months portends a poorer prognosis [29]. Furthermore, larger sample sizes are likely to better characterize the relationship between disconnecting the epilepsy network and changes in neuropsychological functions post-

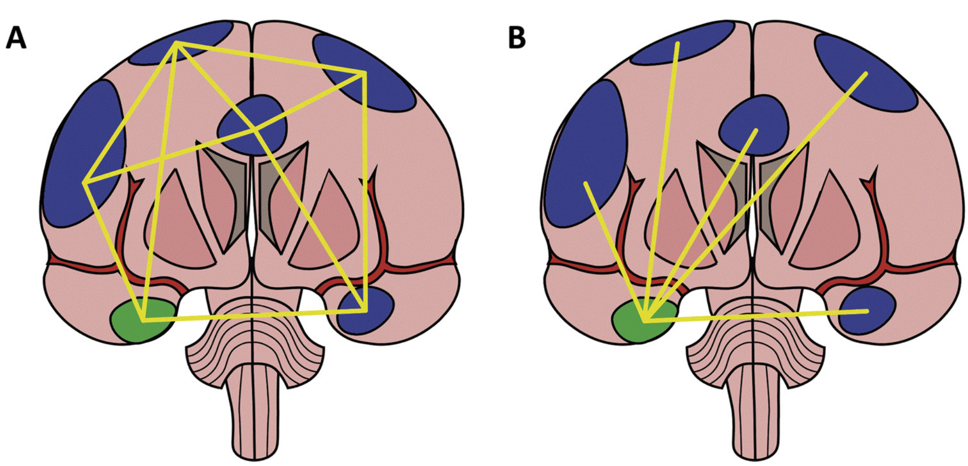

Fig. 6. Network Model Epilepsy networks that are disrupted by surgery may have a different connectivity pattern that is more readily disconnected by removal of the irritative zone. (green: irritative zone, blue: epilepsy resting network, yellow: network connections). The regions shown are not specific to any patient, they are merely shown to illustrate how network connectivity may affect refractoriness to temporal lobe surgery techniques.
A. A hypothetical connectivity map of an epilepsy network is shown that has connections between networked cortical regions that might support epileptic network integration after surgical removal of the irritative zone.
B. Shows the same epilepsy network but with a hypothetical connectivity pattern that would be more readily disconnected by resection of the irritative zone.

operatively and overtime.

While these data are largely consistent with extant literature regarding decline in naming and verbal memory following temporal lobe epilepsy, the declines in this sample have been small and limited sample size prevented analyses for effect of side of surgical resection on neuropsychological scores and percent disconnection. The study is ongoing and larger samples may reveal a more intricate relationship between epilepsy network disconnection and functional temporal lobe network. The series is also small, with the aim of this study is to stimulate future research in this field and further cooperative between comprehensive epilepsy centers.

5. Conclusion

Our epilepsy network modeling algorithm using non-invasive and non-concurrent data modeled patient-specific functional networks related to the irritative zone. Disconnection of these pathologic epilepsy networks was shown to significantly correlate with seizure-free outcomes and relative improvement in naming and memory function.

Author 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.

Disclosure

The authors have no disclosures.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2020.01.018.

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