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Resting state connectivity in neocortical epilepsy: The epilepsy network as a patient-specific biomarker

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HIGHLIGHTS

- Analogous intracranial EEG electrodes were selected across patients with similar seizure onset loci.
- Epilepsy networks were defined and compared across patients.
- Even between patients with similar seizure onsets, epilepsy networks were unique.

ABSTRACT

Objective: Localization related epilepsy (LRE) is increasingly accepted as a network disorder. To better understand the network specific characteristics of LRE, we defined individual epilepsy networks and compared them across patients.
Methods: The epilepsy network was defined in the slow cortical potential frequency band in 10 patients using intracranial EEG data obtained during interictal periods. Cortical regions were included in the epilepsy network if their connectivity pattern was similar to the connectivity pattern of the seizure onset electrode contact. Patients were subdivided into frontal, temporal, and posterior quadrant cohorts according to the anatomic location of seizure onset. Jaccard similarity was calculated within each cohort to assess for similarity of the epilepsy network between patients within each cohort.
Results: All patients exhibited an epilepsy network in the slow cortical potential frequency band. The topographic distribution of this correlated network activity was found to be unique at the single subject level.
Conclusions: The epilepsy network was unique at the single patient level, even between patients with similar seizure onset locations.
Significance: We demonstrated that the epilepsy network is patient-specific. This is in keeping with our current understanding of brain networks and identifies the patient-specific epilepsy network as a possible biomarker in LRE.

1. Introduction

Contrary to its historical roots, localization related epilepsy (LRE) is now increasingly recognized as a network disorder (Bartolomei et al., 2001; Spencer, 2002; van Diessen et al., 2013). With this paradigm shift in our understanding comes the need to reconsider all aspects of how we evaluate and manage patients afflicted with this burdensome disease. Clinicians have historically been trained to identify the seizure "focus", sometimes at the expense of considering the more diffuse pathology implicated in many epileptogenic substrates. However, with increasing recognition of the significance of epilepsy networks, clinicians have the opportunity to reconsider how we care for patients, especially

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those with refractory LRE. The epilepsy network itself may prove to be a previously unrecognized therapeutic target which can be capitalized upon as a potential alternative (or additional) option to consider in the treatment of patients with epilepsy.

Many lessons have been learned regarding the epilepsy network, stemming largely from connectivity analysis using intracranial EEG (Bartolomei et al., 2001; van Dellen et al., 2009; Bandt et al., 2014; Fuertinger et al., 2016), resting state fMRI (reviewed in Waites et al., 2006; Bettus et al., 2009; Liao et al., 2010; Maneshi et al., 2014; Fan et al., 2016; Vaughan et al., 2016; Wirsich et al., 2016; Liu et al., 2017; Xiao et al., 2017), scalp EEG (Vecchio et al., 2015; Balter et al., 2016; Storti et al., 2017), and combined EEG/fMRI (Shamshiri et al., 2017), as well as MEG (Englot et al., 2015; Hsiao et al., 2015; Wang and Meng, 2016) and DTI (Bonilha et al., 2012, 2015; Munsell et al., 2015; Taylor et al., 2015; Fang et al., 2017). However, the majority of this work has investigated the network connectivity of mesial temporal lobe epilepsy (MTLE), with few studies focusing on network interactions related to neocortical epilepsy (Bartolomei et al., 2001; Bandt et al., 2014; Pedersen et al., 2015; Vecchio et al., 2015; Fuertinger et al., 2016; Storti et al., 2017). Further, the bulk of this work has investigated group-level differences between either epileptic brains compared to nonepileptic brains or right versus left MTLE with little consideration of the connectivity profile at the individual level.

Previous work by our group investigated the role of patient-specific resting state networks in neocortical epilepsy. Results from this prior work demonstrate that initial seizure propagation occurs preferentially along the epilepsy network which is defined as cortical regions which are correlated with the seizure onset area in the *interictal state* using intracranial EEG data. This implicates the interictal connectivity profile in the pathophysiology of epilepsy (Bandt et al., 2014). The work presented here expands on those previous findings. Here, we develop a method of electrode selection to compare networks across patients undergoing intracranial EEG for assessment of nonlesional epilepsy. We group patients into cohorts with anatomically restricted seizure onset locations and evaluate a set of common electrode locations within each cohort. The purpose of this is to assess for topographic similarities and differences in interictal connectivity patterns in order to determine whether the distribution of connectivity is guided by similar anatomic location of seizure onset or rather is unique to each individual patient. This work suggests that the epilepsy network for individual patients is often unique even when seizure onsets occur in similar locations across individuals. As a result each patient can be considered fundamentally unique in clinical practice and the composite features of their disease burden considered on a case-by-case basis in order to optimize their treatment plan. In this context, the resting state epilepsy network emerges as an additional variable with which to evaluate and potentially manage patients with refractory epilepsy.

2. Methods

2.1. Subjects

Ten patients undergoing intracranial monitoring for characterization of their seizure foci and whose seizure etiology could not be determined from MRI imaging (i.e. nonlesional epilepsy patients) were included in this study with IRB approval (Yale HIC #0605001482). Patients were selected retrospectively from a single surgeon's clinical experience (DDS). Study subjects were segregated into three cohorts based on the anatomic location of seizure onset. These three cohorts included four patients with seizure onset in the left frontal lobe, four with seizure onset in the left lateral temporal lobe and two with seizure onset in the right posterior quadrant (parietal and occipital lobes). Demographics and clinical information for each subject are outlined in Table 1. Each patient underwent craniotomy for implantation of subdural and depth electrodes. Intracranial electrode placement was guided solely by clinical indications. Following localization and characterization of seizure onset, the patients were brought back to the operating room for removal of intracranial electrodes. Eight patients underwent subsequent resection of their seizure foci. Two patients were not candidates for surgical resection. One of these patient's seizure onset co-localized with expressive speech cortex; extra-operative stimulation mapping identified speech arrest at the seizure onset electrode contact. This patient underwent subsequent responsive neurostimulator implantation. The second patient's seizure onset was located within supplementary motor cortex, but his seizures demonstrated rapid generalization throughout the bilateral hemispheres within milliseconds following onset. This patient awaits thalamic stimulation pending its final approval by the Food and Drug Administration.

2.2. Data collection and seizure onset localization

Following 24–48 h of post-operative recovery in the neurosurgery intensive care unit, seizure monitoring was initiated. Uninterrupted EEG recording and video monitoring proceeded for a period ranging from 6 to 14 days to allow for optimal characterization of patients' seizure onset and initial propagation dynamics. During this period, all anti-epileptic medications were tapered and subsequently discontinued. Intracranial EEG signals were acquired from the implanted electrode array (Ad-Tech Medical Instrument Corporation, Racine, WI, USA) at a sampling frequency of 1024 Hz using a differential amplifier (Natus Medical Incorporated, San Carlos, CA, USA). Signals were referenced to skull facing ground and reference electrodes. The implanted electrodes were comprised of 2.3 mm diameter platinum electrode contacts spaced 10 mm apart embedded in silastic in a grid or strip orientation placed over the cortical surface. Implanted depth electrodes were comprised of 1.1 mm diameter platinum electrode contacts spaced 5 mm apart embedded in silastic placed stereotactically into cortical or subcortical structures. To identify seizure onset locations, the intracranial EEG was reviewed separately, blind to other clinical information, by 2 expert neurologists using traditional intracranial EEG visual analysis. If the reviewers disagreed, they discussed the case to reach a final consensus. Patients were then assigned to cohorts based on the anatomical region of seizure onset zone, with 4 patients with seizure onset in the frontal lobe, 4 patients with seizure onset in the temporal lobe, and 2 patients with seizure onset in the posterior region consisting of parietal and occipital lobes.

2.3. Epoch selection

For each patient, five 10-minute awake but resting (i.e. patient was refraining from purposeful activities), interictal epochs of intracranial EEG data were randomly selected for analysis. These intervals were removed from seizure activity by at least 60 minutes in either direction and did not co-occur with extra-operative cortical stimulation mapping.

2.4. Electrode localization & conversion to atlas space

Pre- and post-operative axial T1 MPRAGE magnetic resonance imaging (MRI) sequences were combined with post-implantation volumetric computerized axial tomography (CT) scan for localizing intracranial electrode contacts using the Bioimage Suite software package (Papademetris et al., 2006). Each electrode contact was localized on post-implantation CT and then co-registered to the

Table 1
Demographics & clinical information.

Patient	Age	Sex	Handedness	Location of seizure onset	Pathology	Duration of epilepsy	Outcome, engel class Engel (1993)
Frontal cohort							
F1	18	F	R	L orbito-frontal	Non-specific gliosis	13 years	IIIA
F2	34	M	R	L frontal	n/a	22 years	IVA
F3	21	M	Ambidextrous	L frontal	Non-specific gliosis	16 years	IIC
F4	23	M	R	L orbito-frontal	n/a	13 years	IIIA
Temporal cohort							
T1	34	M	R	L temporal	Non-specific gliosis	11 years	IVA
T2	34	M	R	L temporal	Non-specific gliosis	5 years	IIIA
T3	30	M	R	L temporal	Non-specific gliosis	10 years	IIIA
T4	53	F	R	L temporal	Non-specific gliosis	14 years	IIB
Posterior quadrant cohort							
PQ1	31	F	R	R Posterior Parietal	FCD Type IIB	16 years	IA
PQ2	31	F	R	R Occipital	FCD Type IIB	23 years	IIB

F = Female; M = Male; L = Left; R = Right; FCD = Focal Cortical Dysplasia.

patients' post- and pre-operative MRI using a two-step co-registration paradigm to optimize accuracy. Co-registered images were manually verified for accuracy by confirming anatomic concordance of brain structures between the different imaging modalities. Following electrode contact localization and image co-registration, all implanted electrode contacts were visualized on subject specific cortical MRI surfaces (Fig. 1). Next, the MNI standard brain (Collins et al., 1994) was co-registered to each subject-specific brain to enable inter-subject comparison. The three-dimensional MNI coordinates for all implanted electrode contacts were then converted into Talairach space for inter-subject comparison.

2.5. Electrode contact selection for inclusion in analysis

Noisy electrode contacts for individual patients were excluded based on visual inspection (1 for patient F3, 1 for patient F4, and 2 for patient PQ1). The location of each remaining implanted electrode contact was transformed into Talairach coordinates in common atlas space. Next, for each cohort of patients (frontal, temporal, and posterior quadrant seizure onset), a data-driven algorithm was used to select electrode contacts in analogous locations across patients within a given cohort. First the patient in the cohort with the fewest number of electrode contacts was chosen as the "reference" patient. Then, for each electrode contact belonging to this reference patient, all electrode contacts within 20 units of Talairach space were found for the remaining patients in the cohort. If all patients had at least one electrode contact available within these parameters, then a cluster was designated. In other words, given a reference patient's electrode contact at (x0, y0, z0) in Talairach space, a cluster would be designated if all other patients had an electrode contact at location (x1, y1, z1) such that $\sqrt{(x1-x0)^2+(y1-y0)^2+(z1-z0)^2} < 20$. Electrodes that were members of clusters found in this manner were included in the set of electrode contacts shared across patients within that cohort. In cases where more than one electrode contact was within 20 units of the reference location, a random choice among possible candidates was made. Finally, clusters were examined manually by a single neurosurgeon (SKB) and clusters that spanned sulci were excluded. In this way, 27 clusters of electrode contacts were designated within the frontal cohort, with each patient having one unique electrode contact assigned to each of these 27 clusters (Fig. 2a). Data from these shared electrode contacts was then used to allow for between-subject comparisons, matched for anatomical region. The same technique was used to identify clusters of similarly located electrode contacts across the temporal (34 clusters) and posterior quadrant (59 clusters) cohorts (Fig. 2b and c). Finally, the seizure onset electrode contact was designated for each patient. In cases where seizure onset was simultaneously localized to more than one electrode contact, a centrally located electrode contact among all identified seizure onset electrode contacts was selected for seed-based analysis.

2.6. Pre-processing

For each shared electrode contact in each patient, we concatenated five 10-minute epochs of raw recorded activity. This concatenation was deemed acceptable because the typical variability of the signal in each epoch far exceeded any differences in the signal average between concatenated segments. This composite time series was then lowpass filtered for frequencies <0.5 Hz to isolate slow cortical potential signals using a sixth order Butterworth filter. After lowpass filtering, time-series data were re-referenced to the common mean by computing the average time-series across electrode contacts selected for inclusion and subtracting this common signal from each electrode contact's time-series.

2.7. Seed-based correlation analysis

Seed-based correlation values for each electrode contact were created by computing Pearson correlation values across all pairs of included electrode contacts (the shared electrode contacts, plus the seizure onset electrode contact) in each patient using bandpass filtered data selecting for the slow cortical potential frequency band. Seed-based correlation values corresponded to a single row (or column) of the final n × n symmetric correlation matrix (where n = number of shared electrode contacts + 1 seizure onset location), with the specific row/column indicating the seed identity (Fig. 3).

2.8. Epilepsy network determination

To designate each patient's epilepsy network, a two-sample Kolmogorov-Smirnov test was performed comparing seed-based connectivity of the seizure onset electrode contact to each of the other included electrode contacts. Those electrode contacts demonstrating a significant difference in correlation compared to the seizure onset electrode were not included in the epilepsy network while those found to be similar were included in the epilepsy network. Results were corrected for multiple comparisons using false discovery rate control, with alpha = 0.05.

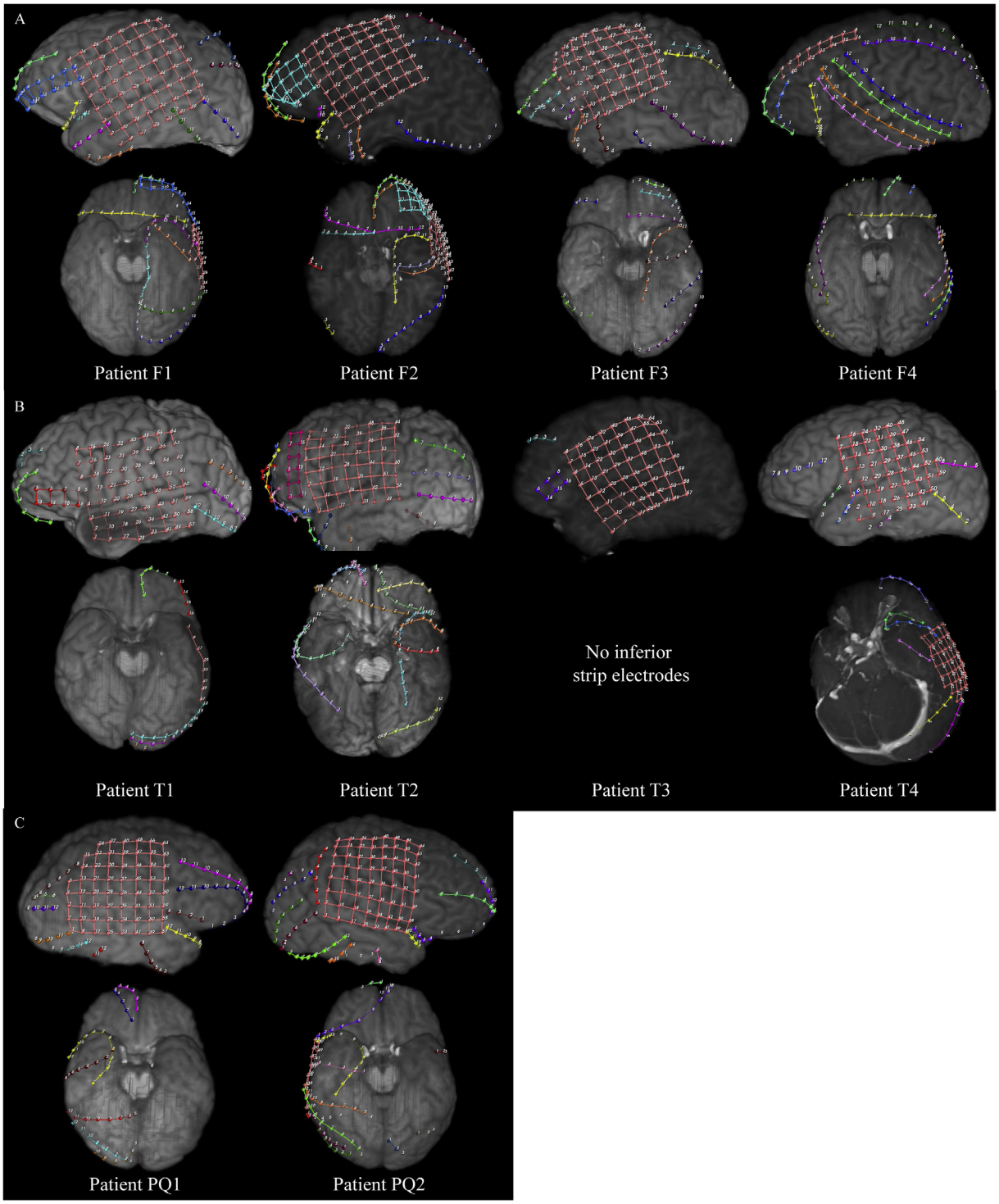

Fig. 1. Patient specific cortical surface reconstructions with implanted electrodes localized in radiographic space. (A) frontal cohort, (B) temporal cohort, (C) posterior quadrant cohort. Note that only surface electrode contacts, not depth electrode contacts, are pictured.

2.9. Between patient comparison

To compare similarity of epilepsy networks between patients within the same cohort, we represented each patient as a vector of *m* Boolean values, where m is the number of electrode contact loci shared across all patients within each cohort. Each entry in the vector was 1 if the locus belonged to the epilepsy network or 0 if the electrode contact did not belong to the epilepsy network. We then computed the Jaccard similarity index between vectors of different patients within each cohort. In order to assess the significance of the similarity measures, we generated a null distribution for Jaccard similarity, which was dependent on the number of shared electrode contacts and the raw number of in-network electrode contacts that each patient possessed. Specifically, for each patient pair that was compared, the patients' vectors were shuffled (element order re-arranged within each vector) randomly 100,000 times and Jaccard similarity index was re-computed to establish the similarity expected by chance. If the Jaccard similarity index

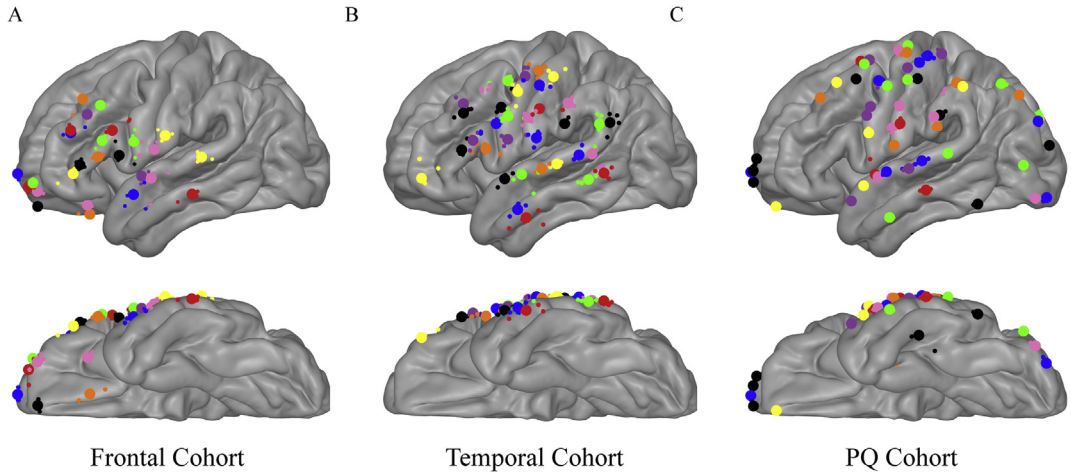

Fig. 2. Topographical distribution of common electrode contact clusters across all patients within each cohort. Each large circle denotes the geometric mean of 1 cluster, and the smaller surrounding circles of the same color show the location of the electrode contacts from each patient that were included in the cluster. Clusters that are comprised of depth electrodes have been projected to the cortical surface. Note that due to the large number of clusters, colors for distinct clusters are repeated. (A) frontal cohort, (B) temporal cohort, (C) posterior quadrant (PQ) cohort.

obtained prior to shuffling fell above the 97.5th percentile or below the 2.5th percentile in the null distribution, then the experimental value was considered significantly similar or dissimilar, respectively.

3. Results

3.1. Resting state network connectivity in epilepsy

Within each cohort, a subset of electrode contacts in analogous locations was selected using a data-driven algorithm as described in Methods. The frontal cohort included 27 shared electrode contacts across four subjects, the temporal cohort included 34 shared electrode contacts across four subjects, and the posterior cohort included 59 shared electrode contacts across two subjects. Fig. 2 depicts these shared electrode contact clusters. Fig. 3 shows seed-based correlation matrices across the shared electrode contacts from each patient. Fig. 4 depicts the in- versus out-of-network assignment for each electrode contact in each patient with in-network assignments indicating inclusion in the epilepsy network.

3.2. Topographic distribution of resting state connectivity within same-lobe foci

Although cohorts included seizure onset locations within the same lobar anatomical region, there was variability in the topographic distribution of the epilepsy network across patients. To quantify this variability, Jaccard similarity was calculated to compare the similarity of the epilepsy network within each cohort and a permutation test was conducted to assess the significance of the similarity between patients. Notably, subjects T1 and T2 both showed an epilepsy network that included all electrode contacts assessed and therefore, a null distribution of similarity indices was not able to be calculated. However, with the exception of these two patients with broadly inclusive epilepsy networks, no two patients within any given cohort demonstrated more overlap in network membership than would be expected by chance. Network membership patterns also differed subjectively across patients, even when patients showed anatomically similar seizure onset locations (for example, subjects T2 and T3 and subjects F2 and F4).

4. Discussion

Using intracranial EEG data acquired during the interictal period from patients undergoing intracranial evaluations for seizure onset localization, we define patient-specific epilepsy networks. We demonstrate that the topographic distribution of functional connectivity in the epilepsy network is unique at the single subject level regardless of the anatomic location of patients' seizure onset. Notably, we also find unique patterns of epilepsy network connectivity even when comparing subjects with nearly identical anatomic locations of seizure onset.

Previous work investigating network connectivity in epilepsy has explored several related but distinct questions. A large number of studies have examined network connectivity features in epilepsy in well-known physiologic resting state networks such as the default mode, perceptual, face processing, and language networks, among others (Zhang et al., 2009; Song et al., 2011; Haneef et al., 2012; Hsiao et al., 2015; Riley et al., 2015; Coito et al., 2016; Liu et al., 2017). Other work has investigated resting state functional connectivity in epilepsy patients using intracranial EEG (Bartolomei et al., 2001; van Dellen et al., 2009; Zaveri et al., 2009; Duncan et al., 2013; Bandt et al., 2014; Fuertinger et al., 2016; Joshi et al., 2016), while others have studied functional connectivity non-invasively using scalp EEG (Vecchio et al., 2015; Balter et al., 2016; Storti et al., 2017), MEG (Englot et al., 2015; Hsiao et al., 2015; Wang and Meng, 2016) or BOLD data acquired via fMRI (reviewed in Waites et al., 2006; Bettus et al., 2009; Liao et al., 2010; Maneshi et al., 2014; Fan et al., 2016; Vaughan et al., 2016; Wirsich et al., 2016; Liu et al., 2017; Xiao et al., 2017). These studies have largely explored temporal lobe epilepsy exclusively, (reviewed in Waites et al., 2006; Bettus et al., 2009; van Dellen et al., 2009; Liao et al., 2010; Cataldi et al., 2013; Maneshi et al., 2014; Hsiao et al., 2015; Vega-Zelaya et al., 2015; Bernhardt et al., 2016; Fan et al., 2016; Vaughan et al., 2016; Wirsich et al., 2016) with many fewer studies exploring other subtypes of epilepsy including neocortical epilepsy (Bartolomei et al., 2001; Vecchio et al., 2015; Storti et al., 2017). Furthermore, the bulk of this prior work has compared connectivity findings in epilepsy against connectivity in healthy controls rather than between patients. A small amount of prior work has examined fMRI functional connectivity and found patient-specific networks in patients with frontal lobe epilepsy, consistent with the results presented

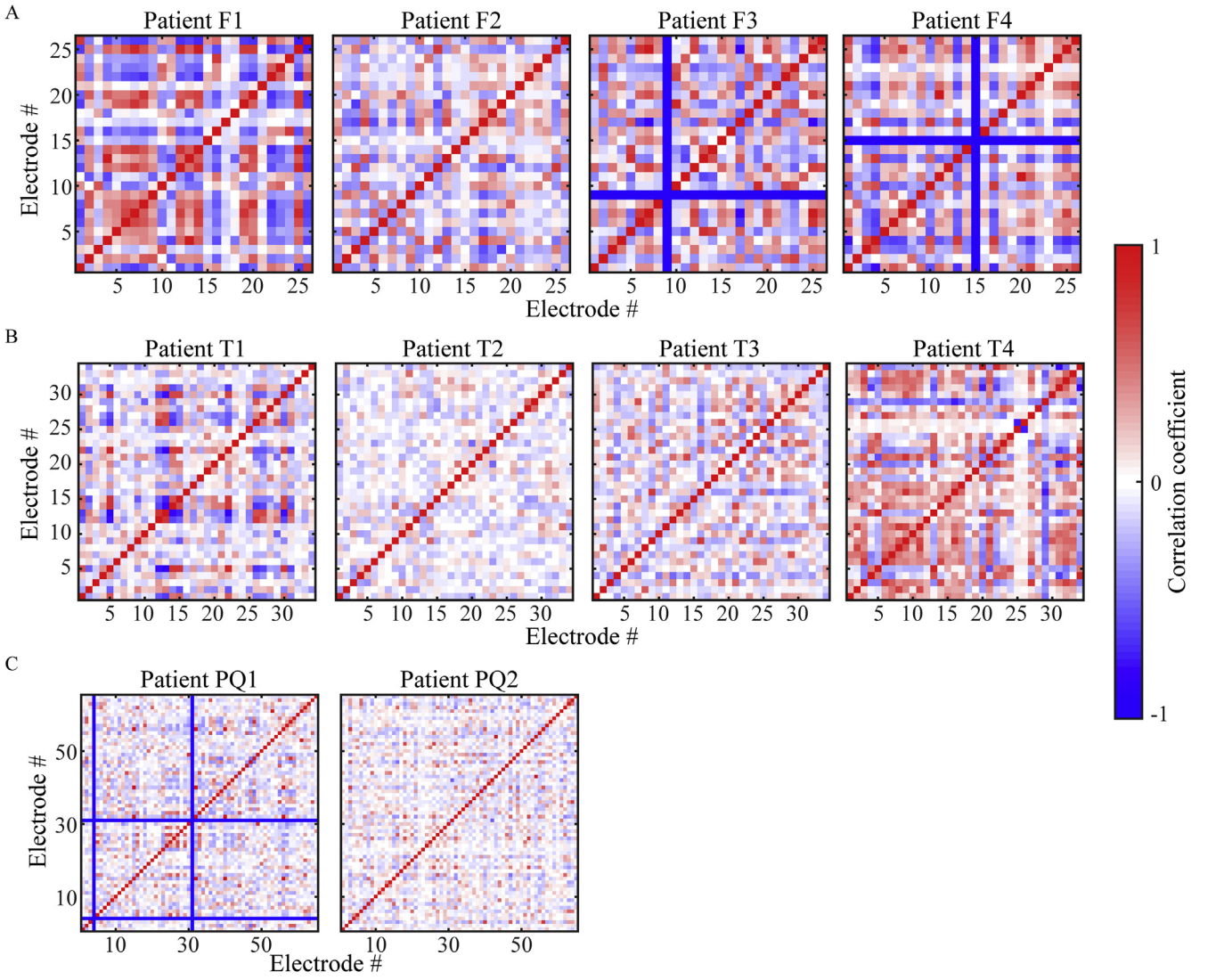

Fig. 3. Correlation matrices for shared electrode contacts across patient cohorts. Each row or column in individual panels depicts the correlation coefficient of one electrode contact with each other electrode contact. The correlation coefficients associated with each electrode contact were compared with the correlation coefficients associated with the seizure focus electrode contact using a Kolmogorov-Smirnov test to determine which electrode contacts fell within the seizure network. The seizure onset electrode contact is number 1 in each patient. Electrodes that were excluded due excessive noise are shown in dark blue. (A) frontal cohort, (B) temporal cohort, (C) posterior quadrant (PQ) cohort.

here using intracranial EEG (Luo et al., 2014). Our findings are also consistent with a previous study using intracranial EEG suggesting that connectivity is patient specific (Maharathi et al., 2016).

Those studies that have examined connectivity patterns in individual patients using intracranial EEG have often done so with the goal of using connectivity patterns to better identify seizure onset locations (Wilke et al., 2009, 2011; van Mierlo et al., 2013), or have characterized patient network similarities using global metrics rather than attempting to select analogous electrodes within patient cohorts (Maharathi et al., 2016). The work presented here is the first to statistically quantify differences using intracranial EEG, and the first to consider the effect of anatomical location of seizure onset on network connectivity patterns. While only examined interictal data were examined here, previous work has shown consistency of networks between ictal and inter-ictal epochs (Wilke et al., 2011; Bandt et al., 2014), and therefore patient specific networks could reasonably be predicted to persist through seizures.

We note that the number of patients presented in this study and within each cohort is small and that dividing patients into cohorts based on the lobe of seizure onset represents a rudimentary way of assigning patients. However, given the heterogeneity of electrode placements, increasing numbers of patients within cohorts necessarily leads to exclusion of electrode contacts, lower numbers of clusters within cohorts, and a decreased ability to compare networks between patients. We believe that the method of electrode selection presented here represents a useful method that may be fruitfully applied to small cohorts of patients with very similar onset locations, such as patients T2 and T3. In addition, brain networks have been previously defined from intracranial or scalp EEG signals using a variety of mathematical methods including calculation of mutual information or Granger causality (Sohrabpour et al., 2016; Chapeton et al., 2017) and graph theoretic measures such as nodal length and clustering coefficients. Lee et al. (2017). However, there is consistency between various methods used to defined functional connectivity (Hassan et al., 2017).

The work presented here is also congruent with recent work of network connectivity in individual healthy subjects. Brain networks have long been defined at the group level and only recently has there been consideration of differences between individual

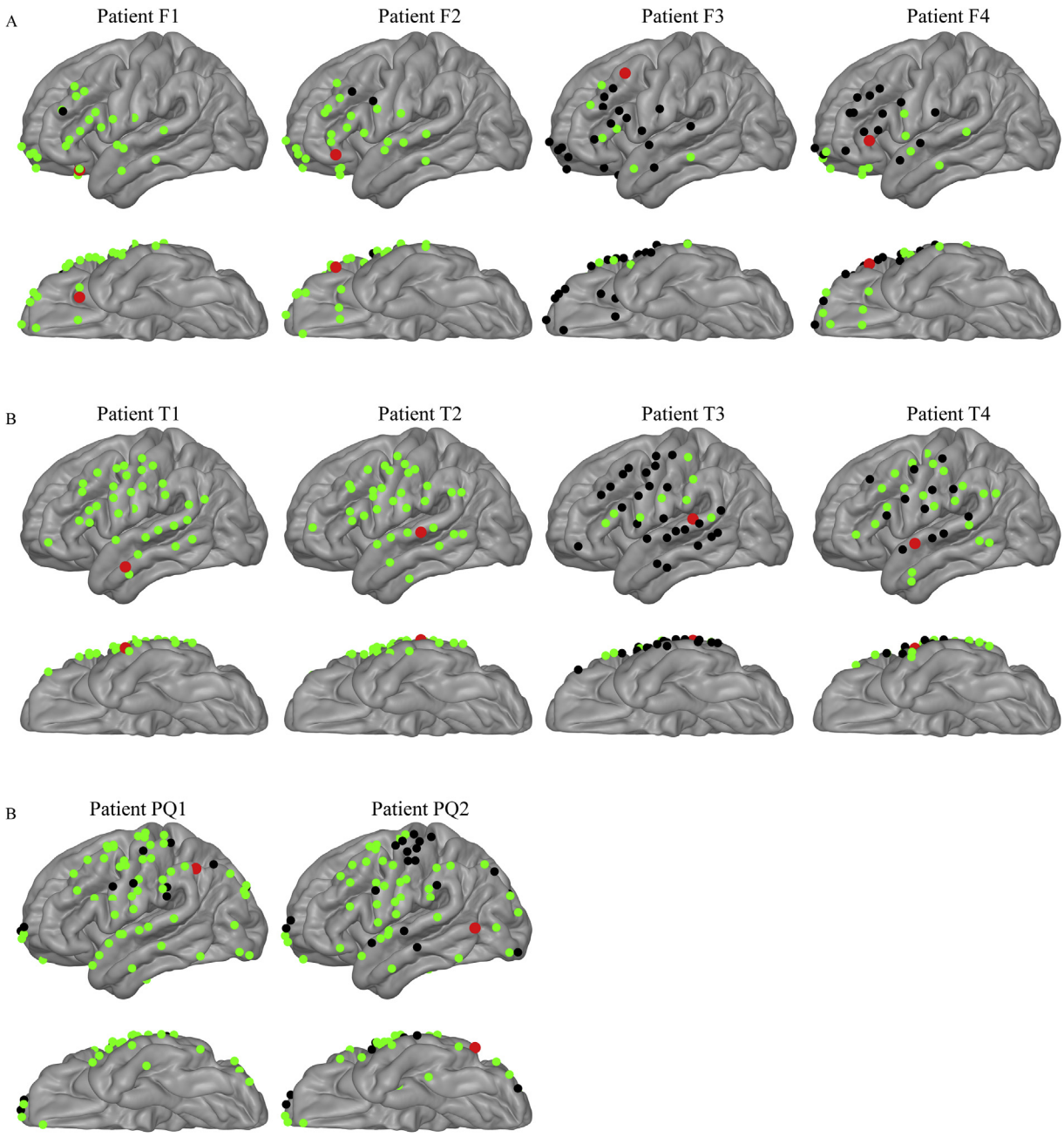

Fig. 4. Surface distribution of epilepsy network membership as determined by seed-based correlation analysis. Seizure foci are shown in red, in-network electrode contacts that are included in the epilepsy network are shown in green, and out-of-network electrode contacts not included in the epilepsy network are shown in black. (A) frontal cohort, (B) temporal cohort, (C) posterior quadrant (PQ) cohort.

healthy subjects (Mueller et al., 2013; Davison et al., 2016). It is important to extend the study of individual differences in functional connectivity to a disease state as varied as epilepsy. Some work in a rhesus monkey model suggests that epileptic networks can vary even when the same anatomical area serves as a seizure focus (Cleeren et al., 2015), but individual variability in human epilepsy patients is much less studied. The unique nature of the epilepsy network at the single patient level suggests that it may play a role in the clinical manifestation of epilepsy either in the context of cognitive and social performance or in the manifestation of epilepsy itself via seizure semiology, peri-ictal phenomena and/or neuropsychological manifestations of the disorder. Furthermore, the identification of the epilepsy network as a unique feature in epilepsy supports the notion of it being a potential additional or alternative therapeutic target. A possible therapeutic strategy for incorporation of the epilepsy network include potentially modulating networks (invasively or non-invasively) in order to restore the epileptic brain to the non-epileptic state using a variety of technologies which are becoming increasingly available. Additionally, the epilepsy network could be considered as a possible tool for patient stratification and prediction of outcomes. This is consistent with the fact that the profile of network connectivity can be used to predict surgical outcomes in patients (Negishi et al., 2011; Antony et al., 2013; Bonilha et al., 2015; Sinha et al., 2017; Tomlinson et al., 2017). Although this concept remains exploratory at this point, it does raise many interesting points for consideration as we evaluate how best to advance the field of epilepsy care in the context of understanding epilepsy as a network disorder.

Here we demonstrate that the epilepsy network, defined in the interictal state, is unique at the single subject level using correlation analysis on human intracranial EEG data. This is in keeping with our evolving understanding of brain networks and identifies the epilepsy network as a possible patient-specific biomarker in LRE. As such, it is conceivable that the epilepsy network may represent an emerging therapeutic target in the management of refractory epilepsy.

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Conflict of interest

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

References

Antony AR, Alexopoulos AV, Gonzalez-Martinez JA, Mosher JC, Jehi L, Burgess RC, et al. Functional connectivity estimated from intracranial EEG predicts surgical outcome in intractable temporal lobe epilepsy. PLoS One 2013;8:e77916.

Balter S, Lin G, Leyden KM, Paul BM, McDonald CR. Neuroimaging correlates of language network impairment and reorganization in temporal lobe epilepsy. Brain Lang 2016. https://doi.org/10.1016/j.bandl.2016.06.002.

Bandt SK, Bundy DT, Hawasli AH, Ayoub KW, Sharma M, Hacker CD, et al. The role of resting state networks in focal neocortical seizures. PLoS One 2014;9:e107401.

Bartolomei F, Wendling F, Bellanger JJ, Regis J, Chauvel P. Neural networks involving the medial temporal structures in temporal lobe epilepsy. Clin Neurophysiol 2001;112:1746–60.

Bernhardt BC, Bernasconi A, Liu M, Hong SJ, Caldairou B, Goubran M, et al. The spectrum of structural and functional imaging abnormalities in temporal lobe epilepsy. Ann Neurol 2016;80:142–53.

Bettus G, Guedj E, Joyeux F, Confort-Gouny S, Soulier E, Laguitton V, et al. Decreased basal fMRI functional connectivity in epileptogenic networks and contralateral compensatory mechanisms. Hum Brain Mapp 2009;30:1580–91.

Bonilha L, Jensen JH, Baker N, Breedlove J, Nesland T, Lin JJ, et al. The brain connectome as a personalized biomarker of seizure outcomes after temporal lobectomy. Neurology 2015;84:1846–53.

Bonilha L, Nesland T, Martz GU, Joseph JE, Spampinato MV, Edwards JC, et al. Medial temporal lobe epilepsy is associated with neuronal fibre loss and paradoxical increase in structural connectivity of limbic structures. J Neurol Neurosurg Psychiatry 2012;83:903–9.

Cataldi M, Avoli M, de Villers-Sidani E. Resting state networks in temporal lobe epilepsy. Epilepsia 2013;54:2048–59.

Chapeton JI, Inati SK, Zaghloul KA. Stable functional networks exhibit consistent timing in the human brain. Brain 2017;140:628–40.

Cleeren E, Casteels C, Goffin K, Janssen P, Van Paesschen W. Ictal perfusion changes associated with seizure progression in the amygdala kindling model in the rhesus monkey. Epilepsia 2015;56:1366–75.

Coito A, Genetti M, Pittau F, Iannotti GR, Thomschewski A, Holler Y, et al. Altered directed functional connectivity in temporal lobe epilepsy in the absence of interictal spikes: a high density EEG study. Epilepsia 2016;57:402–11.

Collins DL, Neelin P, Peters TM, Evans AC. Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J Comput Assist Tomogr 1994;18:192–205.

Davison EN, Turner BO, Schlesinger KJ, Miller MB, Grafton ST, Bassett DS, et al. Individual differences in dynamic functional brain connectivity across the human lifespan. PLoS Comput Biol 2016;12:e1005178.

Duncan D, Duckrow RB, Pincus SM, Goncharova I, Hirsch LJ, Spencer DD, et al. Intracranial EEG evaluation of relationship within a resting state network. Clin Neurophysiol 2013;124:1943–51.

Engel J. Surgical treatment of the epilepsies. 2nd ed. New York: Raven Press; 1993.

Englot DJ, Hinkley LB, Kort NS, Imber BS, Mizuiri D, Honma SM, et al. Global and regional functional connectivity maps of neural oscillations in focal epilepsy. Brain 2015;138:2249–62.

Fan X, Yan H, Shan Y, Shang K, Wang X, Wang P, et al. Distinctive structural and effective connectivity changes of semantic cognition network across left and right mesial temporal lobe epilepsy patients. Neural Plast 2016;2016:8583420.

Fang P, An J, Zeng LL, Shen H, Qiu S, Hu D. Mapping the convergent temporal epileptic network in left and right temporal lobe epilepsy. Neurosci Lett 2017;639:179–84.

Fuertinger S, Simonyan K, Sperling MR, Sharan AD, Hamzei-Sichani F. High-frequency brain networks undergo modular breakdown during epileptic seizures. Epilepsia 2016;57:1097–108.

Haneef Z, Lenartowicz A, Yeh HJ, Engel Jr J, Stern JM. Effect of lateralized temporal lobe epilepsy on the default mode network. Epilepsy Behav 2012;25:350–7.

Hassan M, Merlet I, Mheich A, Kabbara A, Biraben A, Nica A, et al. Identification of interictal epileptic networks from dense-EEG. Brain Topogr 2017;30:60–76.

Hsiao FJ, Yu HY, Chen WT, Kwan SY, Chen C, Yen DJ, et al. Increased intrinsic connectivity of the default mode network in temporal lobe epilepsy: evidence from resting-state MEG recordings. PLoS One 2015;10:e0128787.

Joshi RB, Gaspard N, Goncharova II, Duckrow RB, Duncan D, Gerrard JL, et al. Regional and network relationship in the intracranial EEG second spectrum. Clin Neurophysiol 2016;127:3485–91.

Lee C, Im CH, Koo YS, Lim JA, Kim TJ, Byun JI, et al. Altered network characteristics of spike-wave discharges in juvenile myoclonic epilepsy. Clin EEG Neurosci 2017;48:111–7.

Liao W, Zhang Z, Pan Z, Mantini D, Ding J, Duan X, et al. Altered functional connectivity and small-world in mesial temporal lobe epilepsy. PLoS One 2010;5:e8525.

Liu F, Wang Y, Li M, Wang W, Li R, Zhang Z, et al. Dynamic functional network connectivity in idiopathic generalized epilepsy with generalized tonic-clonic seizure. Hum Brain Mapp 2017;38:957–73.

Luo C, An D, Yao D, Gotman J. Patient-specific connectivity pattern of epileptic network in frontal lobe epilepsy. Neuroimage Clin 2014;4:668–75.

Maharathi B, Loeb JA, Patton J. Estimation of resting state effective connectivity in epilepsy using direct-directed transfer function. Conf Proc IEEE Eng Med Biol Soc 2016;2016:716–9.

Maneshi M, Vahdat S, Fahoum F, Grova C, Gotman J. Specific resting-state brain networks in mesial temporal lobe epilepsy. Front Neurol 2014;5:127.

Mueller S, Wang D, Fox MD, Yeo BT, Sepulcre J, Sabuncu MR, et al. Individual variability in functional connectivity architecture of the human brain. Neuron 2013;77:586–95.

Munsell BC, Wee CY, Keller SS, Weber B, Elger C, da Silva LA, et al. Evaluation of machine learning algorithms for treatment outcome prediction in patients with epilepsy based on structural connectome data. Neuroimage 2015;118:219–30.

Negishi M, Martuzzi R, Novotny EJ, Spencer DD, Constable RT. Functional MRI connectivity as a predictor of the surgical outcome of epilepsy. Epilepsia 2011;52:1733–40.

Papademetris X, Jackowski MP, Rajeevan N, DiStasio M, Okuda H, Constable RT, et al. BioImage suite: an integrated medical image analysis suite: an update. Insight J 2006;2006:209.

Pedersen M, Omidvarnia AH, Walz JM, Jackson GD. Increased segregation of brain networks in focal epilepsy: an fMRI graph theory finding. Neuroimage Clin 2015;8:536–42.

Riley JD, Fling BW, Cramer SC, Lin JJ. Altered organization of face-processing networks in temporal lobe epilepsy. Epilepsia 2015;56:762–71.

Shamshiri EA, Tierney TM, Centeno M, St Pier K, Pressler RM, Sharp DJ, et al. Interictal activity is an important contributor to abnormal intrinsic network connectivity in paediatric focal epilepsy. Hum Brain Mapp 2017;38:221–36.

Sinha N, Dauwels J, Kaiser M, Cash SS, Brandon Westover M, Wang Y, et al. Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. Brain 2017;140:319–32.

Sohrabpour A, Ye S, Worrell GA, Zhang W, He B. Noninvasive electromagnetic source imaging and granger causality analysis: an electrophysiological connectome (econnectome) approach. IEEE Trans Biomed Eng 2016;63(12):2474–87.

Song M, Du H, Wu N, Hou B, Wu G, Wang J, et al. Impaired resting-state functional integrations within default mode network of generalized tonic-clonic seizures epilepsy. PLoS One 2011;6:e17294.

Spencer SS. Neural networks in human epilepsy: evidence of and implications for treatment. Epilepsia 2002;43:219–27.

Storti S, Boscolo Galazzo I, Khan S, Manganotti P, Menegaz G. Exploring the epileptic brain network using time-variant effective connectivity and graph theory. IEEE J Biomed Health Inform 2017;21(5):1411–2142.

Taylor PN, Han CE, Schoene-Bake JC, Weber B, Kaiser M. Structural connectivity changes in temporal lobe epilepsy: spatial features contribute more than topological measures. Neuroimage Clin 2015;8:322–8.

Tomlinson SB, Porter BE, Marsh ED. Interictal network synchrony and local heterogeneity predict epilepsy surgery outcome among pediatric patients. Epilepsia 2017;58:402–11.

van Dellen E, Douw L, Baayen JC, Heimans JJ, Ponten SC, Vandertop WP, et al. Long-term effects of temporal lobe epilepsy on local neural networks: a graph theoretical analysis of corticography recordings. PLoS One 2009;4:e8081.

van Diessen E, Diederen SJ, Braun KP, Jansen FE, Stam CJ. Functional and structural brain networks in epilepsy: what have we learned? Epilepsia 2013;54:1855–65.

van Mierlo P, Carrette E, Hallez H, Raedt R, Meurs A, Vandenberghe S, et al. Ictal-onset localization through connectivity analysis of intracranial EEG signals in patients with refractory epilepsy. Epilepsia 2013;54:1409–18.

Vaughan DN, Rayner G, Tailby C, Jackson GD. MRI-negative temporal lobe epilepsy: a network disorder of neocortical connectivity. Neurology 2016;87:1934–42.

Vecchio F, Miraglia F, Curcio G, Della Marca G, Vollono C, Mazzucchi E, et al. Cortical connectivity in fronto-temporal focal epilepsy from EEG analysis: a study via graph theory. Clin Neurophysiol 2015;126:1108–16.

Vega-Zelaya L, Pastor J, de Sola RG, Ortega GJ. Disrupted ipsilateral network connectivity in temporal lobe epilepsy. PLoS One 2015;10:e0140859.

Waites AB, Briellmann RS, Saling MM, Abbott DF, Jackson GD. Functional connectivity networks are disrupted in left temporal lobe epilepsy. Ann Neurol 2006;59:335–43.

Wang B, Meng L. Functional brain network alterations in epilepsy: a magnetoencephalography study. Epilepsy Res 2016;126:62–9.

Wilke C, Worrell G, He B. Graph analysis of epileptogenic networks in human partial epilepsy. Epilepsia 2011;52:84–93.

Wilke C, Worrell GA, He B. Analysis of epileptogenic network properties during ictal activity. Conf Proc IEEE Eng Med Biol Soc 2009;2009:2220–3.
Wirsich J, Perry A, Ridley B, Proix T, Golos M, Benar C, et al. Whole-brain analytic measures of network communication reveal increased structure-function correlation in right temporal lobe epilepsy. Neuroimage Clin 2016;11:707–18.
Xiao F, An D, Zhou D. Functional MRI-based connectivity analysis: a promising tool for the investigation of the pathophysiology and comorbidity of epilepsy. Seizure 2017;44:37–41.
Zaveri HP, Pincus SM, Goncharova II, Duckrow RB, Spencer DD, Spencer SS. Localization-related epilepsy exhibits significant connectivity away from the seizure-onset area. Neuroreport 2009;20:891–5.
Zhang Z, Lu G, Zhong Y, Tan Q, Liao W, Chen Z, et al. Impaired perceptual networks in temporal lobe epilepsy revealed by resting fMRI. J Neurol 2009;256:1705–13.