Spatial-Temporal Network of Epileptic Spikes in Human Neocortex

BY

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M.S., University of Illinois at Chicago, 2015

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Bioengineering
in the Graduate College of the
University of Illinois at Chicago, 2021

Chicago, Illinois

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This thesis is dedicated to my wife, Shamali Dusane, and my parents, for all their support throughout my Ph.D.

ACKNOWLEDGEMENTS

I want to thank my thesis committee - Dr. James L. Patton, Dr. Jeffrey A. Loeb, Dr. John R. Hetling, Dr. Tanya Berger-Wolf, Dr. Marvin Rossi, and Dr. David J. Mogul for their support and guidance. I thank Dr. Eishi Asano, Dr. Anna Serafini, Dr. Rick Smith, Dr. Jorge Rodriguez Fernandez, Dr. Richard Wlodarski, Dr. Jing Hua for their research collaboration on ideas, helping understand the intricate clinical details, and foremost, educating me through this interdisciplinary work.

I probably cannot thank enough Dr. James L. Patton, Dr. Jeffrey A. Loeb for their immense support, constant guidance, regular meetings, brainstorming sessions, and tolerating stupid questions. I also would like to acknowledge the financial support I received throughout my doctoral grant from the National Institute of Health, Sturge-weber foundation, CURE (Citizens United for Research in Epilepsy), and the Department of Bioengineering at UIC.

I want to thank all the members of the MOLECULAR AND TRANSLATIONAL NEUROLOGY LABORATORY, Fabien, Fei, Fozia, Sarah, Joe, Alison, Brinda, Rachel, Liu, Mitch, and Giri for making it a fun place to work. I have special appreciation for Terenda, whom I cannot thank enough.

Most of all, I would like to thank friends and individuals for their immense support.

Biswajit Maharathi

Contribution of Authors

Biswajit Maharathi (BM), along with Jeffrey Loeb (JL) and James Patton (JP), conceived the idea. Anna Serafini (AS) helped direct ideas for clinical applicability. BM designed the studies and performed all the necessary analysis.

Shruti Bagla (SB), Eishi Asano (EA), JL, and BM collected data. BM worked on data cleaning, organization and made it ready for analysis.

BM developed signal processing tools, and Jing Hua (JH) created image analysis tools. Richard Wlodarski (RW) performed image processing. BM conducted all the signal processing, analysis, and image processing.

BM wrote all the manuscripts. JL, JP, EA, SB, RW wrote parts of documents, reviewed, and edited. All authors discussed the results and contributed to the final manuscript.

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LIST OF ABBREVIATIONS

AIC	Akaike information criterion
AU	Arbitary Unit
AUC	Area Under the Curve
CREB	cAMP response element-binding protein
CT	Computed Tomography
dDTF	direct Directed Transfer Function
DTF	Direct Transfer Function
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
ECoG	Electrocorticography
EEG	Electroencephalography
FO	Foramen Ovale
HFO	High Frequency Oscillation
HS	Hippocampal Sclerosis
IIS	Interictal Spike
KPSS	Kwiatkowski–Phillips–Schmidt–Shin
MAPK	Mitogen-activated protein kinase
MRI	Magnetic Resonance Imaging
MVAR	Multivariate Autoregressive Model
PDC	Partial Direct Coherence
PET	Positron Emission Tomography
ROC	Receiver Operating Characteristic
SEEG	Stereo EEG
SOZ	Seizure Onset Zones
SPECT	Single Photon Emission Computed Tomography
TLE	Temporal Lobe Epilepsy

ABSTRACT

Epilepsy, a condition manifested by aberrant brain networks from a combination of disparate etiologies, is in continuing need for better biomarkers for diagnosis and treatment. While seizures identified using electrophysiological tools is most recognized in detecting seizure onset and spread, their rare occurrence limits its ability to identify epileptic foci. On the other hand, events such as interictal spikes are a potential and commonly suggested alternative. Although these spikes are often associated with seizure onset regions, their precise roles are poorly understood. Additionally, the convoluted structural abnormalities alter the way the brain communicates amongst its different regions. What is needed is an integrated approach to understanding the functional networks of the diseased brain that accounts for its underlying structures. Using a combination of long term electrocorticography recordings and magnetic resonance imaging, we developed a set of algorithms and mapped the spatial-temporal network of interictal spike propagations and related it to brain topography and cortical lesions loci in 43 pathologic brains. We found that our method of isolating the time-epochs when time-locked interictal spikes were occurring led to the best identification of seizure onset regions, are related to brain topography, and are related to lesion loci. From a series of work, we have found the following observations. Interictal spike network is highly reproducible at different time points and frequency bands. While spikes are mostly closer to the epileptic foci, they are also sparsely distributed across the neocortex amongst which only a subset of spikes propagate to different cortical regions. Among these propagating spike regions, the spike onset regions often do not correspond to high spiking regions. While spike onset regions partially co-localize to seizure onset regions, they are also found on other cortical regions not identified as seizure onset zones. The specificity of these spike network is significantly higher compared to total brain network which is evaluated using the entire dataset irrespective of spiking.

The spike propagation is not uniform across all cortical region and is dependent on the geodesic distance between electrodes as well as the sulcal patterns. While the total brain network connection density decreases with geodesic distance, the rate of decrease in propagation density for spike network is more drastic. The large sulci such as central sulcus acts as a rigid barrier of propagation and restricts 80% of the propagations. While brain topography is a natural barrier of propagations, the pathologic lesions also play an important role. The spike networks are often found reverberating in the perilesional regions and

colocalize with seizure onset. Such evaluations delineate the relationship between subtle electrical signatures and the underlying pathology, suggesting further attention to these biomarkers to enable better surgical precision, treatment plans, and drug development.

I. INTRODUCTION

Epilepsy is a chronic neurological disorder characterized by recurrent seizures, affecting 70 million people worldwide across every age group, resulting in comorbidity and poor quality of life(Singh and Trevick 2016). Epilepsy differs from other neurological disorders due to its heterogeneity in etiology and phenotypes. It can be classified as either symptomatic where the cause may be an infection in the brain (e.g. neurocysticercosis), brain tumor, stroke, head injury, congenital abnormalities; or it can be idiopathic with no identifiable cause. It is a non-contagious neurological condition, with lifelong comorbidities, poor quality of life, social stigma, and discrimination. Although, 70% of the patients can achieve seizure control with anti-seizure medications, for many drug-resistant patients alternative course of action is necessary for disease control where accurate identification of the epileptic foci is absolutely essential along with adequate knowledge of the functional transmission of signals amongst regions in the brain, known as the epileptic network. Numerous studies have already helped in identifying these seizure onset regions using widely used electrophysiological techniques such as electroencephalography (EEG) combined with imaging. Although seizure source localization uses both manual and algorithmic identification, pinpointing seizure onset regions has never been easy due the different spatio-temporal patterns and the complex mechanisms of seizure initiation. Very few studies explore the mechanisms of seizure onset. The sporadic nature of the seizures also adds additional difficulty. What is needed is the ability gain more information about these complex patterns, structure, and function.

1.1. Electrophysiological events in epilepsy

Seizures are hallmark of epilepsy. These are abrupt, highly synchronized, rhythmic spatio-temporal neuronal activity that often alters the brain's natural state for several hours (Karoly et al. 2016). Extensive research has been performed on seizure onset, spread to different cortical regions and its relationship with epileptic foci (Miao, Tang, et al. 2014; Bartolomei et al. 2016; Bandt et al. 2014; S.-A. Lee, Spencer, and Spencer 2000; Wilke et al. 2010; Worrell et al. 2004; Dai et al. 2012). Multiple seizures recorded from individual patients help understanding the seizure affected cortical regions and leads to identify the pathological cortex responsible for seizure generation. However, seizures are infrequent events, making epileptic foci identification based on seizure onset alone difficult. Evidence suggests that abnormal brain

networks are not only confined to seizures but in fact, there are more frequent interictal events (events in between two consecutive seizures) produced by this pathological network such as interictal spikes, sharp waves, high frequency oscillations (A Korzeniewska et al. 2014; Staba, Stead, and Worrell 2014). Amongst these interictal events, interictal spikes are defined as brief electrographic transients of approximately 250ms or less, consisting of a short sharp wave, followed by a lasting slow wave (K. J. Staley, White, and Dudek 2011; K. J. Staley and Dudek 2006; de Curtis and Avanzini 2001). These interictal spikes are considered as significant biomarkers of epilepsy and widely found in seizure onset and other brain regions (Asano et al. 2004; Hufnagel et al. 2000; Marsh et al. 2010; Asano et al. 2003; Kobayashi, Merlet, and Gotman 2001). While decades of research establish the importance of interictal spikes in epilepsy, the functional dynamics of these paroxysmal events and its relationship with seizure and epileptic foci is poorly understood. There are also varied opinion on the role of interictal spikes suggesting, interictal spikes may also have a significant, yet independent impact on behavior as they are present in a wide variety of neuropsychiatric disorders in the absence of seizures (G. L. Holmes and Lenck-Santini 2006; Nicolai and Kasteleijn-Nolst Trenité 2011; Ebus et al. 2012; Baglietto et al. 2001). Previous studies have suggested that the increase in occurrence of interictal spiking protects the brain against seizures (Lieb et al. 1978; Lange et al. 1983; de Curtis and Avanzini 2001). However recent studies suggest otherwise. While some studies suggest that the spikes play a functional role in developing the epileptic foci (K. Staley, Hellier, and Dudek 2005; White et al. 2010; K. J. Staley and Dudek 2006), and resection of high spiking cortical regions improve post-surgical outcomes; Others suggest that spike occurrence is not a reliable predictor of seizure onset regions (Asano, Brown, and Juhász 2013). This conflicting evidence leads us to believe that spike occurrence alone may not be a functionally useful measure, and further analysis of interictal spikes including their source activity, network pathways of propagation and network characterization are necessary to develop a better understanding of the role of interictal spikes in epilepsy.

1.2. Methods of evaluating the brain connectivity

Brain network are often measured in three different but related connectivity measures. Structural connectivity reflects the synaptic connections connecting anatomically distinct brain regions through the white matter tracks. These connections are the physical brain connections and are often stable. Diffusion-weighted and diffusion tensor imaging (DWI/DTI) are the neuroimaging techniques used to find the fine

scale brain microstructures and structural abnormalities such tumor, necrosis, edema, and other lesion pathologies. While structural connectivity is highly stable and provides a true sense of brain connections, it lacks the time varying measures of connectivity. On the other hand, functional connectivity provides the statistical estimations of the time varying connectivity. Several neuroimaging techniques such as fMRI, EEG, MEG is used to calculate the functional connectivity. Since it is a statistical measure of the connections between different brain regions irrespective of the presence of physical connection, it often needs appropriate statistical validations. There are several parametric and non-parametric methods that calculates the functional connectivity in time and frequency domain. While correlation, coherence and partial coherence-based studies have revealed the pairwise functional connections [1], and more recently multivariate algorithms such as Direct Transfer Function and Partial Direct Coherence use parametric modelling to robustly identify causal propagations. We prefer Granger causality-based direct directed transfer function (dDTF) to evaluate the functional causal networks. This method has been used extensively and proven to identify the most likely direct connections in a multivariate environment (Fasoula, Attal, and Schwartz 2013; Anna Korzeniewska et al. 2008; Hur and Kim 2015; Laura Astolfi et al. 2007; Bianchi et al. 2013; Biswajit Maharathi et al. 2018). Using these functional networks, we have understood that the pathologic functional networks are very consistent (Biswajit Maharathi et al. 2018; Biswajit Maharathi, Loeb, and Patton 2016). When these causality-based algorithms are combined with structural connectivity measures, it is called effectivity connectivity that reflects the effect of one cortical region exerted on other brain regions. Once such connectivity measures are estimated, graph theory-based measures are used to characterize the structural and functional connections in normal and pathologic brain.

1.3. Approaches to evaluate epileptic connectivity

Epileptic events are spontaneous and appear intermittently across the neocortex. In network evaluation of epileptic signal, when all the electrode data is looked together without giving preference to any specific epileptic events or brain location, it is difficult to distinguish which propagations represent background activity and which are pathologic. Previous study suggest that usually different brain regions within neocortex frequently communicate with each other (Biswajit Maharathi, Loeb, and Patton 2016) making it difficult to isolate the pathologic propagations from the background ones. Epileptic brain also often does

not spike uniformly across times and cortical regions. Spike can be seen localized to specific brain regions and occur repetitively over time in some of those specific location raising a question regarding the distinct characteristics of these event specific network patterns and their reliability on locating the epileptic brain regions as compared to the underlying background network interaction of all the brain regions.

1.4. Impact of brain topography on the functional network of propagations

Dynamic brain networks represent the spontaneous interaction of different brain regions. Previous connectivity studies suggest that although unique functional networks are produced during spontaneous and task related activity, they are not entirely a product of it. The resilient brain topography that represents the physical connections of the certainly delineates the spontaneity of such networks (Park and Friston 2013; Honey, Thivierge, and Sporns 2010; Zalesky, Fornito, and Bullmore 2010). Previous studies have presented that the structure influences functional propagation, irrespective of disease, time of recording or electrophysiological frequency band (Biswajit Maharathi et al. 2018; Biswajit Maharathi, Loeb, and Patton 2016; Park and Friston 2013). Although there are studies that outline the influence of brain structure on its spontaneous functional connections, what is needed is an approach that evaluates the functional connectivity while also considering the underlying structure. When the functional connectivity is integrated with structural measure such as cortical thickness, geodesic distance, and the brain topography, combined with statistical methods, we can establish the relationship between interictal spike-epoch propagation occurrence and geodesic distance. Also, it is essential to understand the role of large sulci and gyri in changes in connectivity density, however they have not been extensively researched. The words “functional network” are typically used to distinguish the statistically evaluated propagation behavior amongst electrodes, and “structural network” are used to distinguish the detailed anatomical considerations such as white matter pathways and geodesic path distances over the brain topology.

1.5. Brain lesions and interictal spike

Structures such as gyri and sulci are the hardwired communication pathways within brain topography that controls the information exchange while transmitting information from one cortical region to the next one. While these structures help brain to control the brain’s natural order of information flow, brain lesions

are the pathological abnormalities that disrupt this order. These structural lesions are associated with partial epilepsy and are often clinically intractable. These lesions can be small or may cover large portions of the brain. While lesions such as stroke, tumor or vascular malformation have higher favorable outcome for seizure control, other abnormalities such as hippocampal sclerosis negatively impacts the outcome. Although there is a general clinical consensus on the expected outcome, the exact role of structural abnormalities towards outcome is not clearly understood. While clearly demarcated lesions may be associated with recurrent seizures and may have stronger prognostic influence on outcome, the association needs extensive investigation.

The relationship between lesion location and epileptic foci is also not straight forward. While many times seizure onset is confined within the lesion and perilesional boundaries, in many patients the seizure foci can be far away and, in some cases, distinct and non-contiguous with the lesion loci. In the event of secondary epileptogenesis, independent epileptogenic foci are found that are responsive for similar paroxysmal events as observed on or near the structural lesions, although these scenarios are often found in case of tumors. While seizure onset may not be associated with these lesion locations and the epileptic foci, frequent interictal spikes are observed in these areas, however the frequency of the spikes may be dependent on the type of lesion, severity of the disease, cellular alternation and other confounding variables. A previous study suggests that peritumoral regions have frequent spiking with shorter durations but higher power spikes as compared to distant regions and have proved that tumor proximity results in smaller sharper spikes irrespective of the epileptogenic potential of the cortex. Careful surgical planning for lesion loci or seizure foci may result in better outcome, but the prognostic value of these locations is not clearly understood. While complete surgical removal of lesion or epileptic foci results in better seizure control, the combined prognostic value of these parameters may not significantly alter the outcome. A better understanding of the lesion location and epileptic foci is essential for developing rational therapeutic strategies (Awad et al. 1991; Semah et al. 1998; van Breemen, Wilms, and Vecht 2007; Mittal et al. 2016).

1.6. Organization of the thesis

The current work seeks to explore the intricate details of interictal spike, their occurrent at specific brain regions, the causal propagation, and evaluates different graph properties at different electrophysiological

frequency bands. I further evaluate the different between the pathological spike network and the background brain network, evaluate the candidacy of interictal spike network as a potential predictor of epileptic foci. Since topography of the brain and brain lesions play a significant role in delineating the propagation pathways, I have tried to integrate these natural and pathological structural information to the functional one to understand the way a pathological brain function.

The chapters presented below each represent a paper that has been published as part of my thesis work. The above studies are outlined in following 5 chapters, are either been published or are in preparation to be submitted as manuscripts to journals. At first, I characterize the interictal spike network and test their reliability in predicting the epileptic foci (Chapter 2, published in Clinical Neurophysiology). Then I explore the advantage of these networks over background network which is evaluated using the all the recorded signals irrespective of whether they are spiking (Chapter 3, published in the 2019 9th International IEEE/EMBS Conference on Neural Engineering (NER)). I further investigate the role of brain topography in delineating the functional network connections (Chapter 4, published in the 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)). Lastly, I establish relationship between pathological lesion and interictal spike network (Chapter 5, manuscript in preparation to submit to annals of neurology). Finally, my results are further discussed in detail to develop future vision for a better understanding of the functional activity of a pathologic brain (Chapter 6, manuscript in preparation to be submitted to annals of neurology).

II. INTERICTAL SPIKE CONNECTIVITY IN HUMAN EPILEPTIC NEOCORTEX

This chapter has been adapted from the following manuscript publication:

Maharathi, Biswajit, Richard Wlodarski, Shruti Bagla, Eishi Asano, Jing Hua, James Patton, and Jeffrey A. Loeb. "Interictal spike connectivity in human epileptic neocortex." Clinical Neurophysiology 130, no. 2 (2019): 270-279.

2.1. Introduction

Epilepsy is a common neurological disorder characterized by chronic and recurrent seizures. Seizures are abrupt, temporal and spatial patterns of highly synchronized, rhythmic electrical activity that are often followed by a long duration of an altered brain state (Karoly et al. 2016). Due to the clinical importance of seizures in epilepsy and its ramifications resulting in behavioral changes, extensive research has been performed on seizures, its network and the relationship of seizure onset with epileptic foci (Miao, Tang, et al. 2014; Bartolomei et al. 2016; Bandt et al. 2014; S.-A. Lee, Spencer, and Spencer 2000; Wilke et al. 2010; Worrell et al. 2004; Dai et al. 2012). However, seizures are not frequent events, which makes the identification of epileptic foci using seizure onset alone difficult. Evidence suggests that abnormal brain networks are not only confined to seizures but in fact, there are more frequent interictal events (events in between two consecutive seizures) produced by this pathological network (A Korzeniewska et al. 2014). Amongst these interictal events, interictal spikes are defined as brief electrographic transients of approximately 250ms or less, consisting of a short sharp wave, followed by a lasting slow wave (K. J. Staley, White, and Dudek 2011; K. J. Staley and Dudek 2006; de Curtis and Avanzini 2001). These interictal spikes were previously thought to be significant biomarkers of epileptic brain regions along with seizures (de Curtis and Avanzini 2001). Although, vast literature exists on interictal spikes in the epileptic brain, little is known about the dynamic network of these events and their relationship to seizures. While spikes often originate from synchronously firing neurons at or near seizure onset zones (Asano et al. 2004; Hufnagel et al. 2000; Marsh et al. 2010; Asano et al. 2003), they are also observed in cortical regions far from seizure onset (Kobayashi, Merlet, and Gotman 2001; Hufnagel et al. 2000). Moreover, clinically, interictal spikes may not only be a biomarker of epileptic brain regions, and may also have a significant, yet independent

impact on behavior as they are present in a wide variety of neuropsychiatric disorders in the absence of seizures (G. L. Holmes and Lenck-Santini 2006; Nicolai and Kasteleijn-Nolst Trenité 2011; Ebus et al. 2012; Baglietto et al. 2001).

Interictal spikes have also been postulated to play a role in the formation of epileptic foci that produce seizures (K. Staley, Hellier, and Dudek 2005; White et al. 2010; K. J. Staley and Dudek 2006), and animal models have shown that spike generation often precedes the development of seizures (White et al. 2010). The resection of high-spiking cortical regions also has been associated with decreased seizure events and an improved post-surgical outcomes (Tomlinson et al. 2016; Asano et al. 2009; Palmini et al. 1995; Asano et al. 2003). Conversely, other studies challenge this concept, suggesting that increased spiking actually protects the brain against seizure activity (Lieb et al. 1978; Lange et al. 1983; de Curtis and Avanzini 2001). Recent investigations of spike occurrence (frequency) and its correlation with seizure onset regions, have produced conflicting interpretations of whether spike occurrence is a reliable predictor of seizure onset zones (Asano, Brown, and Juhász 2013). This suggests that spike occurrence alone is not a functionally useful measure, and further analysis of interictal spikes including their source activity, network pathways of propagation and network characterization are necessary to develop a better understanding of the role of interictal spikes in epilepsy.

Here, we use an effective connectivity measure to map the causal network behavior of interictal spikes across different cortical regions in the human epileptic brain. Causal connections were computed using direct-directed transfer function (dDTF). We analyzed the dynamic nature of interictal spike networks over time in different patients across a wide range of frequency bands. We further assessed the effects of deep brain sulci, such as the central sulcus, on propagation patterns. Finally, we performed an initial evaluation on the relationships between interictal spike networks and physician identified seizure onset regions.

2.2. Materials and methods

2.2.1. Patient selection and data collection

Ten pediatric epileptic patients (4F/6M, age: 2-15years) with drug-resistant focal seizures were selected under a protocol approved by the institutional review board of Wayne State University and the

University of Illinois at Chicago (Table2.1). All the patients were identified as having intractable epilepsy and underwent surgical implantation of subdural recording electrodes for long-term seizure monitoring at the Children's Hospital of Michigan, Detroit, Michigan.

Table2.1. Patient clinical information

patient	***age***	***sex***	***diagnosis***	***total spikes in 10 mins***	***seizure focus***
Ep162	1	F	Polymicrogyria	6927	Left Hemispheric
Ep164	3	F	White matter gliosis, superficial heterotopia	4274	Left Temporal Occipital
Ep165	3	F	Mild gliosis	4475	Left Hemispheric
Ep169	8	M	Mild gliosis	3731	Right Occipital-Temporal
Ep181	13	M	Subcortical band heterotopia.	5664	Left Temporal
Ep187	5	M	Tuberous sclerosis	4202	Left Frontal
Ep196	2	M	Patchy subcortical myelinated fiber loss and gliosis	1427	Left Frontal-Temporal-Parietal
Ep198	3	F	Gliosis	631	Left Frontal-Parietal
Ep199	2	M	Gliosis and patchy foci of decreased myelin	1980	Right Temporal
Ep202	3	M	Tuberous sclerosis , and mild patchy cortical gliosis	6467	Right Temporal

The electrocorticography (ECoG) recordings were obtained using a 192 channel Nihon Kohden Digital System (Nihon Kohden America Inc, Foothill Ranch, CA, USA) with 1000 Hz sampling rate from subdural electrodes (4 mm in diameter and spaced 10 mm apart, PMT platinum electrodes, PMT Corporation, Chanhassen, MN, USA). An experienced electroencephalographer help identify three 10-minute interictal ECoG recording segments for each patient. These segments patients were all awake but in quiet restfulness in the resting state (closed eyes, wakeful, and at least 6 hours apart from any seizure activity). We obtained MRI scans for constructing 3D models of each patient's brain using Freesurfer software (B. Fischl and Dale 2000; Bruce Fischl, Sereno, and Dale 1999; Dale, Fischl, and Sereno 1999). We localized and co-registered Electrodes on the 3D brain model using post electrode implantation CT images, and verified electrode locations with the help of intraoperative photographs taken at the time of grid removal (to ensure they did not move (Nakai et al. 2017). We then computed geodesic distances (tracking along the gray-white junction) between electrode positions and cortical thickness measures were computed (J. Wang et al. 2014; Zou et al. 2006).

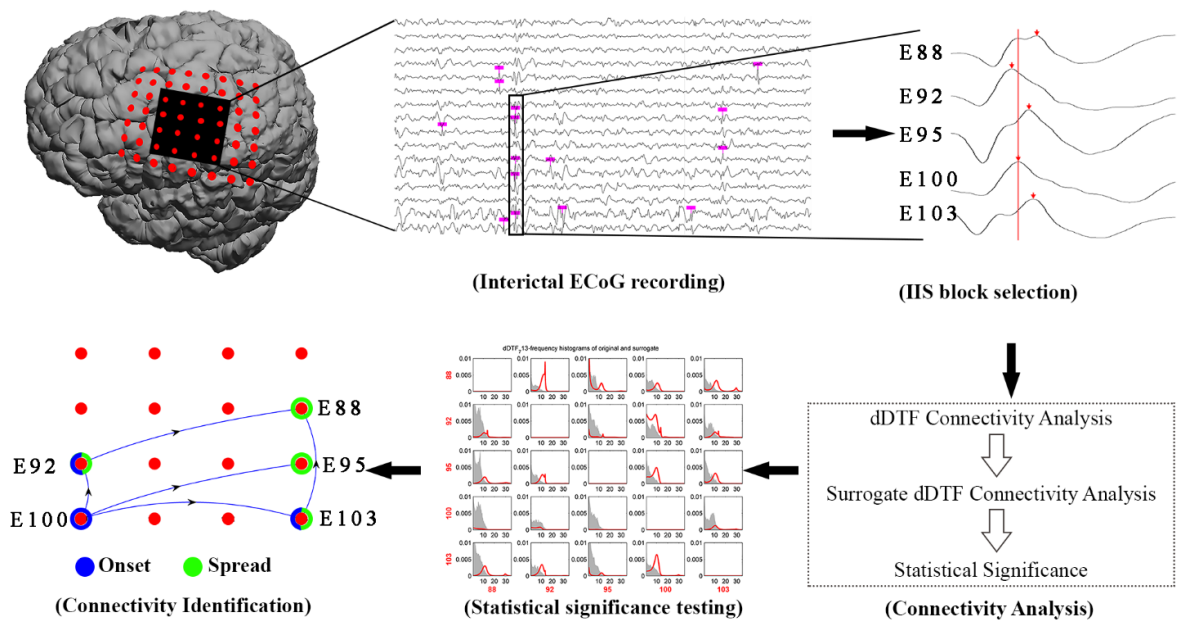


Figure 2.1. Discrete short time direct directed transfer function (dDTF) computing propagation of synchronous interictal spikes. For a selected set of electrodes corresponding to a specific part of the brain, interictal ECoG recording segments were selected and interictal spikes were identified. The dDTF method was applied to synchronously appearing interictal spikes (IIS block selection) to evaluate their propagation activity (connectivity analysis), followed by statistical significance testing using a surrogate data method. In this matrix, the greater the area under the red line for each pair of electrodes that is outside the gray areas corresponds to a significant propagation. Interictal spike onset and spread electrodes were identified based on the frequency of outgoing and incoming propagations for each electrode (connectivity identification, represented by the blue arrows).

Seizure onset zones (SOZ), as previously defined (Asano et al. 2009) were identified from intracranial recordings by an experienced epileptologist (EA). Each patient presented focal clinical or electrographic seizures along with complex epileptic behaviors, except for two patients where only subtle/minimal clinical symptoms were noted during the seizure events. Moreover, five out of ten patients also had epileptic spasms (Asano et al. 2005; Nariai et al. 2011). All patients had neocortical epilepsy often with mild pathological gliosis except for an individual with tuberous sclerosis and another with polymicrogyria.

2.2.2. Signal Analysis

For the purpose of the present study, we focused only on a subset of the electrodes, specifically a 64 channel (8x8) grid placed on the frontal-parietal lobe overlying the central sulcus, to understand the interictal

spike behavior with a common reference and the role of the central sulcus in the propagation of epileptic spikes. For our causal propagation analysis, we did not include other electrode locations that, in some cases, limited our ability to include all seizure onset and spiking areas for this analysis.

We processed these 64 ECoG signals through a multistage algorithm to evaluate the propagation of interictal spikes. We first identified interictal spikes using an established spike detection algorithm and manually validated these results with a trained epileptologist (JAL) and a panel of human reviewers (Daniel T Barkmeier et al. 2012). Then, we isolated synchronous interictal spikes (peaks within 50 ms). We identified time blocks containing these synchronous spikes from 100 ms prior to and 250 ms after all spike peaks, excluding channels without interictal spikes.

2.2.3. Discrete short-time direct directed transfer function (dDTF) analysis and statistical validation

Post extraction, the time blocks were then processed for multivariate causality analysis using discrete short time direct directed transfer function (dDTF). dDTF is a Granger causality based model designed for quasi-stationary signals (M. J. Kamiński and Blinowska 1991; Kuś, Kamiński, and Blinowska 2004). This method predicts the direct flow of information between a pair of signals in the presence of all other signals in a multivariate environment, not confounded by any indirect causal interaction from other signals for a short time period. Prior to the signal processing for causality evaluation, the extracted spike epochs were tested for stationary nature using Phillips–Perron test (~96.5% of spikes found stationary with $p<0.3$) and Kwiatkowski–Phillips–Schmidt–Shin (KPSS) test (~90% of spikes found stationary with $p<0.1$). The isolated spike epochs were then processed for the dDTF evaluation following the recently described method by our group (Biswajit Maharathi, Loeb, and Patton 2016). Briefly, each spike epoch was fitted to a multivariate autoregressive model (MVAR) using modified covariance method to the form $\mathrm{X(t)} = \sum_{\mathrm{i=1}}^{\mathrm{mord}} \mathrm{A(i)X(t-i)} + \mathrm{E(t)}$, where X(t) is the data vector, A(i) is the model coefficient, E(t) is the zero mean uncorrelated white noise, and mord is the order of the model fit. The model order was determined using Akaike information criterion (AIC), where model order of the fit corresponds to the model order with the minimum AIC value (max model order was fixed to 20, however the median model order across all patients was 8±6, mean spikes in each epoch 4±5).

Then the data model is transformed to frequency domain using the Z-transform for a specific frequency band of interest and the power spectra of the signal is calculated as $S(f) = H(f)VH^*(f)$, where V is the variance of the Noise matrix and H(f) is the transfer matrix. Following this, we computed two parameters, partial coherence as $\chi_{ij}^2(f) = \frac{m_{ij}^2(f)}{m_{jj}(f)\, m_{ii}(f)}$, where m_{ij} is the minor of the spectral matrix after removing the ith row and j^{th} column; and full frequency normalized direct transfer function (ffDTF) as $\eta_{ij}^2(f) = \frac{|H_{ij}|^2}{\sum_f \sum_{c=1}^{m} |H_{ic}(f)|^2}$. The direct directed transfer function is evaluated as the linear product of partial coherence and ffDTF. It provides direct causal influence of jth channel on i^{th} channel in the presence of all other channels and has values between 0 and 1. The above process was repeated for all such epochs of synchronous interictal spikes identified in the previous step. To understand the causal propagation of interictal spikes at each frequency band, the isolated spike epochs were processed through the dDTF algorithm for a specific frequency band, including low frequencies (1-50Hz), delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), gamma (30-50 Hz) and high-frequency oscillations (HFO, 80-250 Hz).

We used surrogate data validation to determine the significance of each causal connection (Pritchard, Duke, and Krieble 1995). Briefly, time blocks were transformed to the frequency domain using Fourier transform and the phase values were randomized. Post randomization, the data was transformed back to the time domain and processed for dDTF evaluation as mentioned above using same model parameters. The surrogate data method was repeated 100 times. The surrogate data dDTF estimation serves “false positive” level where no causal relationships among different electrode positions for the given dataset. If dDTF values were greater than the 95th percentile of these surrogate dDTF simulations, we declared this a causal propagation between electrodes (Biswajit Maharathi, Loeb, and Patton 2016). To understand how each patient’s data was consistent across time, we also determined similarity amongst their three 10-minute epochs (pairwise using a Pearson correlation coefficient). These values were normalized to a maximum of causal propagations to further evaluate the network activity of interictal spiking. An alpha level of 0.05 established statistical significance.

2.3. Results

2.3.1. Interictal spike propagation was highly reproducible

Using three 10-minute segments selected from each of 10 patients with neocortical epilepsy, we used an established spike detection algorithm to detect all spikes in all channels independently under an 8x8 subcortical grid centered over the central sulcus (Daniel T Barkmeier et al. 2012). A trained electroencephalographer validated the accuracy of this algorithm for each patient. Next, clusters of interictal spikes within defined time periods were evaluated for synchrony; at least two peaks falling within 50-milliseconds of each other was considered a synchronous event. The dDTF was then used to identify causal propagations (Fig. 2.1).

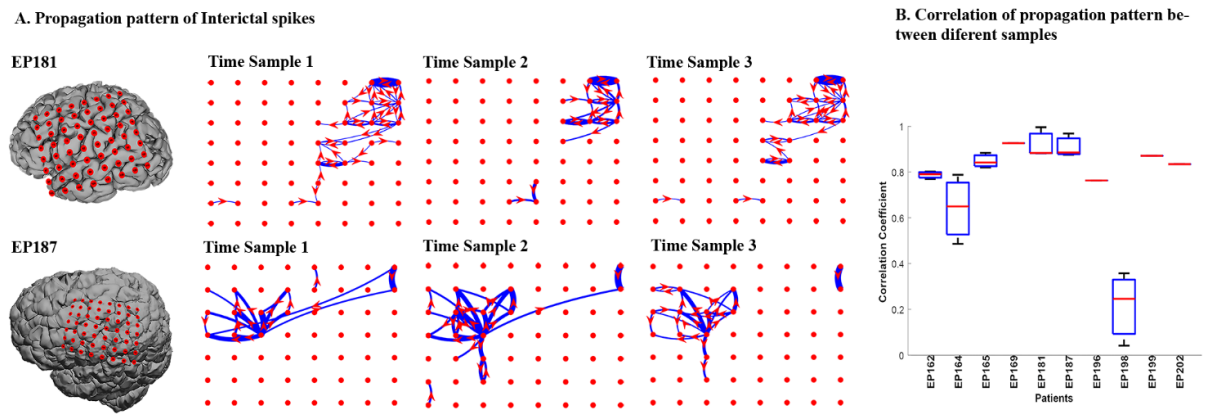


Figure 2.2. Each patient has unique but highly consistent pattern of interictal spike propagation. (A) Shows consistent Interictal spike propagation for three 10 min time segments collected over three different days for 2 patients (EP187, EP181). The red circles are the electrodes positions, and the blue lines represent direct propagation from one electrode to the other in the direction of the arrow in red. The thickness of each blue line corresponds to the frequency of occurrence of propagation events for that pair of electrodes. Only the top 5% of propagations are shown for improved visualization. Including all does not change the pattern. (B) Pairwise Pearson correlation coefficients for 10 patients shows a high level of propagation consistency between three different time samples for each patient except one (ep198). Data shown represent Pearson correlation coefficients between onset patterns of three different 10 minute ECoG segments for each patient. The mean correlation coefficient values for each patient are (0.79, 0.64, 0.85, 0.93, 0.92, 0.91, 0.76, 0.21, 0.87, 0.83) corresponding to patient IDs as shown.

This approach was robust, reproducible, and revealed highly consistent causal propagation patterns of interictal spiking within each patient when evaluated at three different time segments (Fig. 2.2). Interestingly, along with being conserved, these dynamic network patterns were unique to each patient. Pearson correlation coefficients were used to measure the degree of correlation of the propagation patterns within each patient. For this, the number of onset propagations were summarized for each electrode within the selected electrode grid for individual 10-minute ECoG segments. For each patient, the Pearson correlation coefficient was calculated for the corresponding electrode between each pair of 10-minute ECoG files. In 9 out of 10 patients, a patient wise high correlation was observed in onset patterns across the multiple ECoG segments (mean 0.83±0.09) (Fig. 2.2B).

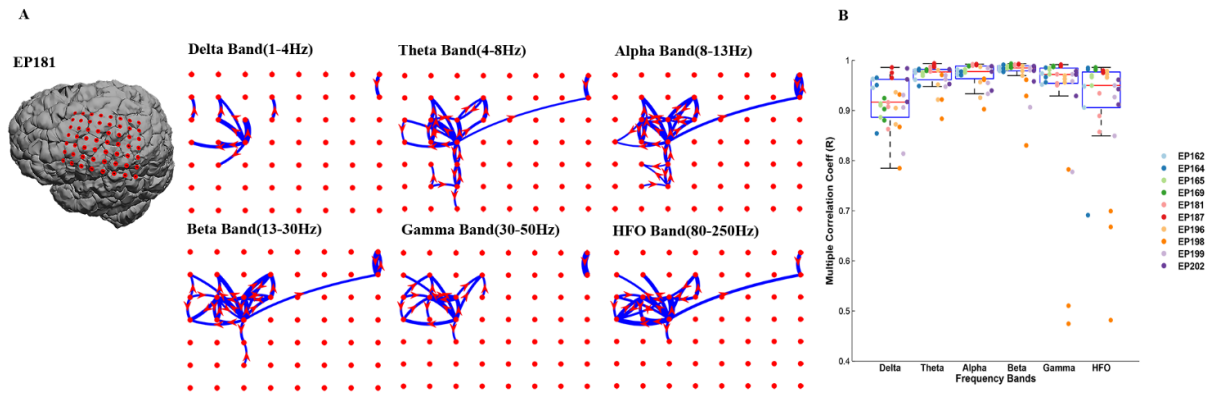


Figure 2.3. Interictal spike propagation is highly consistent across EEG frequency bands. (A) Interictal spike propagation patterns were analyzed across different frequency bands (delta, theta, alpha, beta, gamma and high frequency oscillations). Highly consistent propagation patterns were observed within each frequency band. As an example, spike propagation patterns across different frequency bands for EP187 shows high levels of consistency. (B) This is a box plot superimposed on scatter plot showing multiple correlation coefficients among frequency bands revealing high significance for all 10 patients. Data presented within each box shows the multiple correlation coefficient value for each frequency band with all other frequency bands. Each column in a box represents a single patient and each marking within the column represents the multiple correlation coefficient for 10-minute ECoG. The mean ± SD for each frequency are (Delta: 0.9±0.05, Theta: 0.94±0.04, Alpha: 0.96±0.03, Beta: 0.96±0.04, Gamma: 0.92±0.13, HFO: 0.94±0.05)

2.3.2. Propagation patterns were consistent across all frequency domains

An important area of research involves the role of epileptic activities in different frequency domains, where some studies suggest that higher frequency oscillations have good predictive values for epileptic brain foci (Höller et al. 2015; Miao, Xiang, et al. 2014; Burnos et al. 2014; Frauscher et al. 2017). Here we examined

the propagation pattern for each patient focusing on specific frequencies and found that each frequency band measured had the same propagation pattern (Fig. 2.3). Using the same three 10min ECoG samples, we summarized the number of onset propagations from each electrode in the selected grid. Once evaluated, we calculated the multiple correlation between onset patterns of different frequency bands for corresponding electrodes in each 10-minute ECoG segment for each patient. We found high onset correlation values for each frequency domain (delta=0.92±0.03, theta=0.97±0.01, alpha=0.98±0.01, beta=0.98±0.01, gamma=0.96±0.02, HFO=0.94±0.03 in mean± SD) (Fig. 2.3A). Counting propagations in each frequency band (delta= 1430.3±1697.9, theta= 3131±3322.5, alpha= 3846.8±3051.3, beta= 4389.1±3061.5, gamma= 4707.4±4221.3, HFO= 3990.2±3888.9 count/10 minutes) suggests that beta was most "spike propagation active" followed by the gamma and HFO frequency bands. The total number of propagations in each frequency band across patients varied with patient EP198 having fewest propagations (delta= 73, theta= 207, alpha= 219, beta= 163, gamma= 49.6, HFO= 72).

2.3.3. Regions of spike onset did not correspond to regions with the highest spike occurrence

Most studies to date have focused on rate of spike occurrence (frequency) as a measure of the epileptogenicity of a given brain region, with regions exhibiting the highest spike occurrence considered to be more epileptic. Along with spike occurrence, we analyzed the spike onset regions. Spike onset regions are defined as brain regions which have the greatest number of outgoing spike propagations above a defined maximum threshold within the selected grid. Interestingly, we did not find interictal spike onset regions to have the highest occurrence of spikes (Fig. 2.4A). In fact, electrodes with the highest spike occurrence were more likely to receive spikes from multiple brain locations. Out of all interictal spikes investigated, only 71.3±17.7% of spikes were found present in the selected synchronous spike epochs, and not all synchronous spikes propagated. We isolated spike propagation events in each frequency band, and a small proportion propagated while also shifting frequency (delta= 25±12.8%, theta= 45.1±16.5%, alpha= 51±16.5%, beta= 51.9±18.7%, gamma= 44.2±22.7%, HFO= 47.2±23.6%). Only a small percentage of total locations acted as onset zones (delta= 7.9±3, theta= 10.9±3, alpha= 10.7±3.4, beta= 11.5±3.6, gamma= 12.2±5.6, HFO= 8.6±3.2). Many spikes participated in spread of interictal spike patterns (delta=13.4±7.4, theta= 20.3±8.8, alpha= 17.5±7.4, beta= 14.2±6, gamma= 9.7±4.2, HFO= 16.9±9.5), and hence were "intermediaries" of propagation, having incoming and outgoing events (delta= 3.7±3, theta= 14±6.5, alpha=

22.8±8.8, beta= 26.2±11.2, gamma= 22.3±14.7, HFO= 21.7±15.6). In summary, dDTF analysis suggests that most cortical epileptic spiking brain regions are receiving rather than generating interictal spikes. Furthermore, only a small proportion of spike onset regions brain areas truly initiate spiking, as most act as intermediary regions that both receive and spread the spike to other areas ($p \leq 0.05$ across all frequency bands, pairwise t-test).

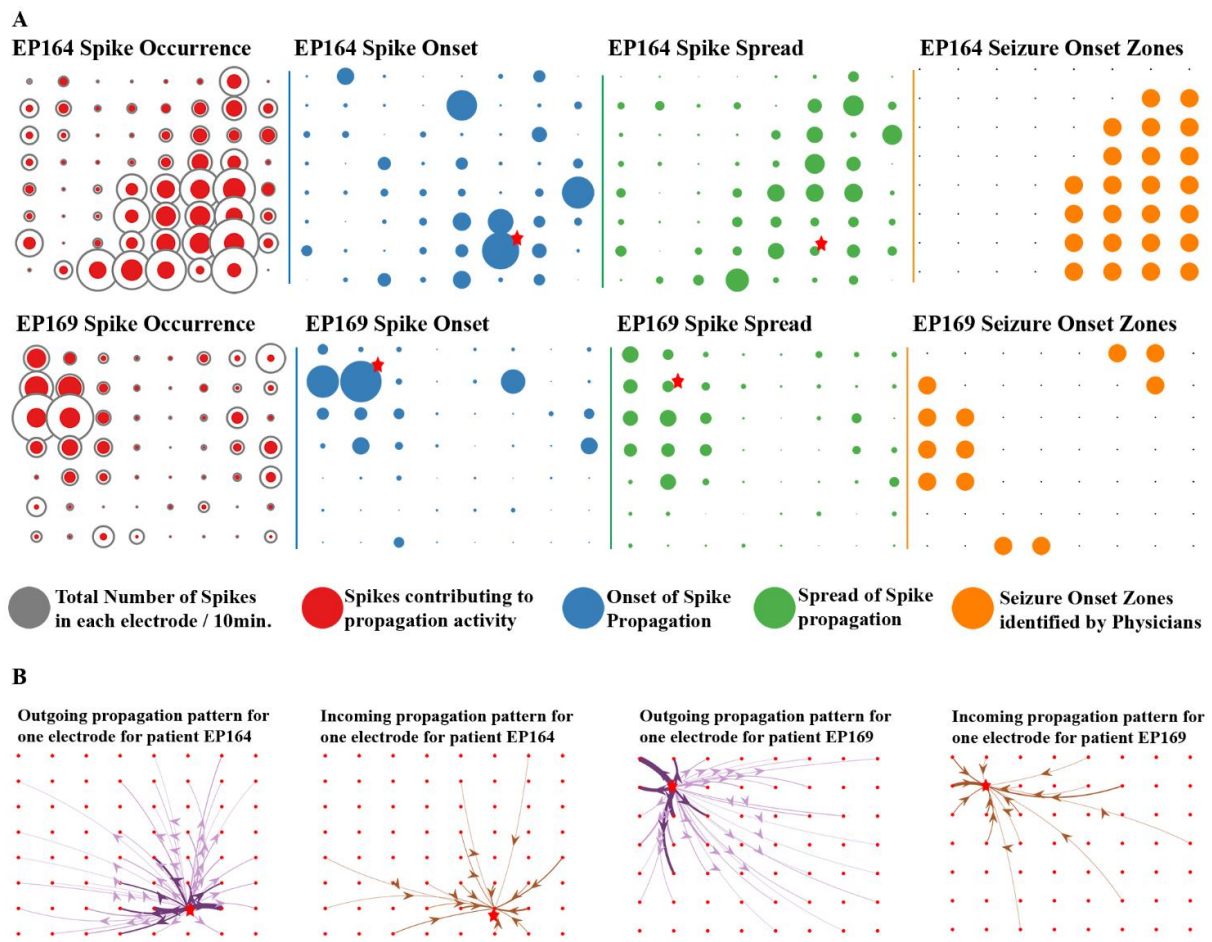


Figure 2.4. Spike onset measurements reveal clear, localized patterns of outgoing and incoming connectivity. (A) Comparison of spike occurrence, onset, and spread demonstrates that measuring spike propagation, presents a simpler, more focused pattern than spike occurrence (left panel) for two patients (EP164, EP169). The size of each circle (red, blue, green) corresponds to the number of events at each electrode location on the 8x8 grid. Propagating spikes are shown as either outgoing (onset) or incoming (spread) and represent only a subset of all spiking events. These results show that spike onset brain regions are most often not the highest spiking (occurrence) regions. (B) The maximal onset electrode for each patient is labeled with □ in A and is shown with detailed outgoing and incoming propagation patterns in B. The thickness of each line corresponds to frequency of propagation and the darker shaded lines on the outgoing propagation plot correspond to a greater than 50% of outgoing propagation from that electrode.

Based on these findings, we developed spatial models of outgoing (spike onset) and incoming (spike spread) epileptic activities as shown in Fig. 2.4B. Isolating individual electrodes on the grid shows highly consistent patterns of both outgoing and incoming activity, providing a unique look at the epileptic connectivity of these brain regions. dDTF analysis therefore allows a deeper understanding of the cortico-cortical networks that underlie interictal spiking which could have important downstream value in improving surgical outcomes in patients with epilepsy.

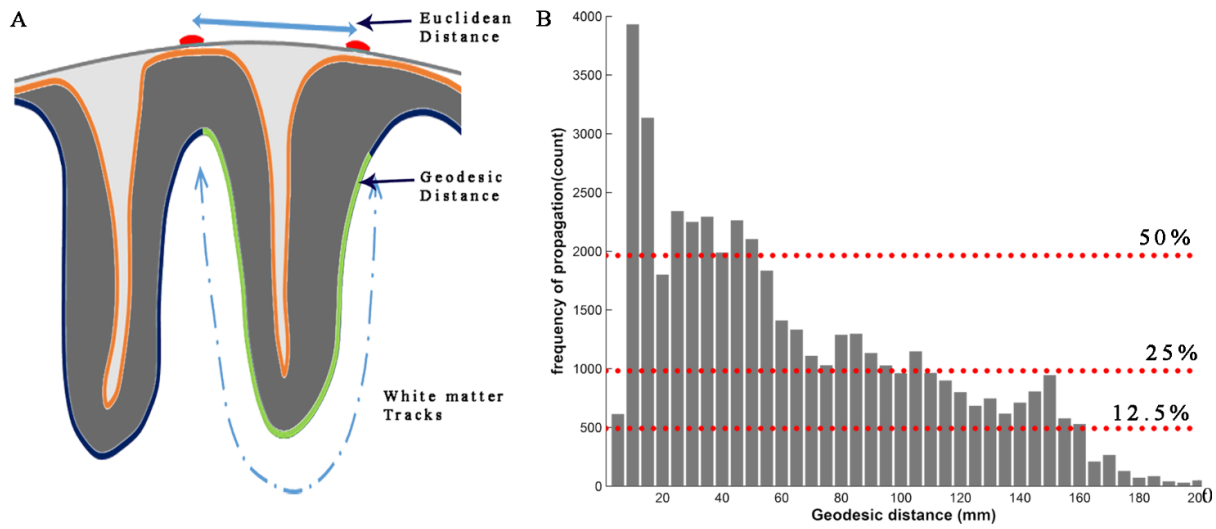


Figure 2.5. Interictal spikes propagate mostly over short geodesic distances, but also travel to distant sites. Most of the interictal propagation is observed between electrodes with short geodesic distances. (A) This shows a 2D surface view of a cortical gyrus. While Euclidian distances are measured on the cortical surface, the geodesic distance is measured though white matter tracks. (B) This is a histogram showing the number of propagation events observed with increasing geodesic distance pooled from all 10 patients. The absolute distance values are rounded off to nearest 5 or multiple of 5. The frequency of propagation events decreases as a function of geodesic distance, but spike propagation can occur at all distances, including regions far from the onset point.

2.3.4. Spatial patterns of interictal spike propagation related to cortical structures

We next combined the temporal and directional patterns of interictal spikes using dDTF with 3D brain models for each patient to understand how brain structure influences spike propagation. Fig. 2.5 shows that while approximately 50% of outgoing spike propagations travel to nearby, often adjacent electrodes (~50 mm geodesic distance), the other half of spikes propagate over longer distances. Surprisingly, approximately 22% of spikes propagated over 10 cm (geodesic) distance from their site of

onset. In addition, the directionality of spike propagation was non-random and affected by cortical topography (Fig. 2.6). Since all patients had an electrode grid overlying the central sulcus, we determined the relative number of spike propagations that crossed the central sulcus versus electrode locations on the same side of central sulcus. Surprisingly, a majority (76±9.6%) of spike propagations did not cross the central sulcus, in either frontal or parietal lobes. This result was also independent from ECoG frequency bands.

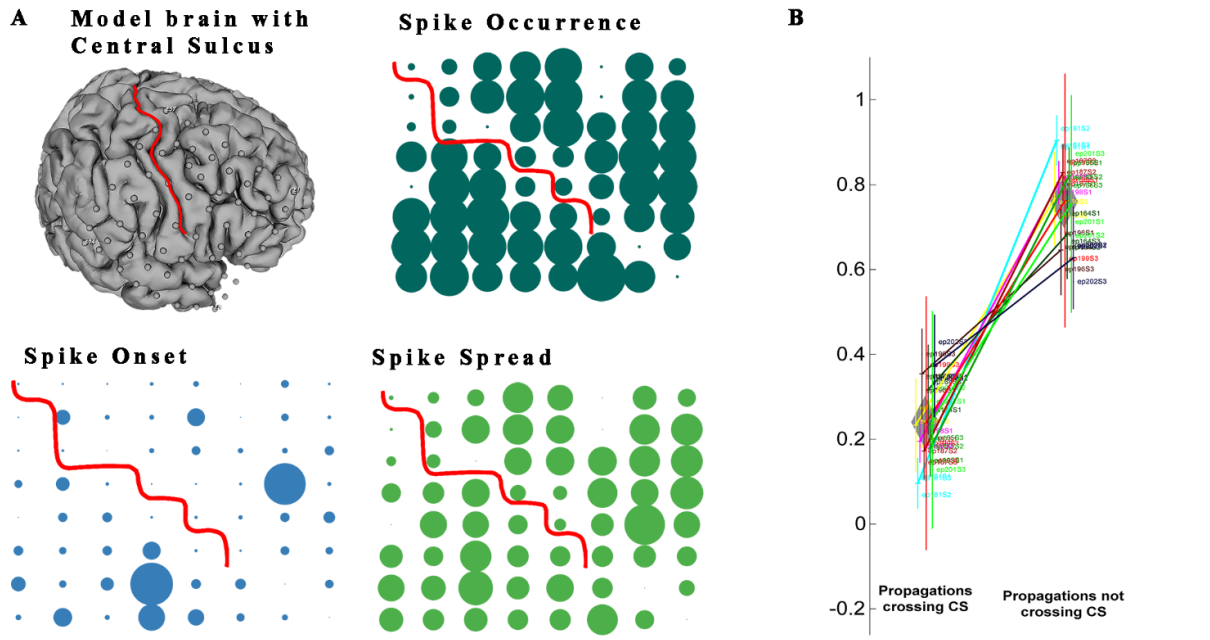


Figure 2.6. The central sulcus acts as a significant barrier to the propagation of interictal spikes. (A) A distinct reduction in activity of spikes, spike onset and spike spread is noted across the central sulcus (CS). This pattern suggests that the central sulcus acts as a natural barrier that restricts spikes from crossing in all patients we examined. (B) Quantitatively there is a proportionate reduction of propagations across the central sulcus. This figure compares the proportion of propagations crossing the central sulcus versus the number of propagations staying on the same side of the sulcus. Solid lines represent the difference between propagations crossing the CS vs not crossing with $p<0.05$. Each vertical line with three points on it represents one patient with results from three ECoG files. The height of the line is the variance between three data points. The width of the diamond shape represents the variance of mean of number of propagations crossing or not crossing the CS across all patients and the height of the diamond shape represents the variance of variance of propagation crossing or not crossing the CS across all patients.

2.3.5. Spike and seizure onsets regions were not often interrelated

Even though interictal spikes are considered prominent biomarkers of epileptic brain regions that also produce seizures (Palmini et al. 1995), their exact spatial and temporal associations with seizures are not

well understood. We investigated whether seizure onset regions had any association with the onset or spread of interictal spiking brain regions. We first considered electrodes with activity exceeding 80% of maximum of the entire grid in at least one of the three files. Fischer's exact test along with Chi-square tests of independence was used to test for any relation between seizure onset regions and (1) interictal spiking regions (2) spike onset regions and (3) spike spread regions. In patient Ep164, there was a strong relationship between seizure onset and interictal spiking regions, spike onset regions, and spike spread regions that were all significant ($p<0.05$). However, in the remaining 7 patients, the spike network had a more complex relationships, if any, with seizure onset regions (Fig. 2.7). For example, in patient Ep169, seizure onset overlapped more with high spiking regions compared to spike onset and spread regions whereas in patient Ep199, seizure onset regions were well associated with spike onset and spread regions ($p< 0.05$). In patients Ep165 and Ep196, who also had infantile spasms, seizure onset regions were diffuse an encompassed a large portion of the grid. Further analysis will be required to understand fully the relationships between spike onset and seizure onset, especially in patient with infantile spasms who often have both diffuse as well as focal seizure onset regions. Two of the patients (Ep181 and Ep187), had their seizure active zones outside of the measurement grids and were therefore removed from consideration. However, even in these patients, the spike onset and spread regions were located on the electrodes near seizure onset regions.

2.4. Discussion

We performed a novel effective connectivity analysis using dDTF to better understand the spatial-temporal patterns of interictal spike propagation in the human epileptic neocortex. We observed consistent pattern of interictal spike propagation which are individualized for each patient and are highly reproducible across multiple days of recording for the same patient. We also found that spikes propagate in a similar fashion across a wide range of frequency bands, including HFOs. Our findings shed new light on the relationships between cortical anatomy and spike propagation. Specifically, propagations often travelled locally, also across great distances but rarely and the central sulcus appears to be a significant barrier for interictal spike propagation which is in congruent with previous studies reporting that signal propagation often skips the motor area (Iimura et al. 2017). Surprisingly, brain regions with the highest spike

occurrences most often did not initiate spiking. While our study was primarily focused on spike onset, we found no clear relationships between interictal spike onset regions and seizure onset regions, suggesting that spikes and seizures might be having different networks.

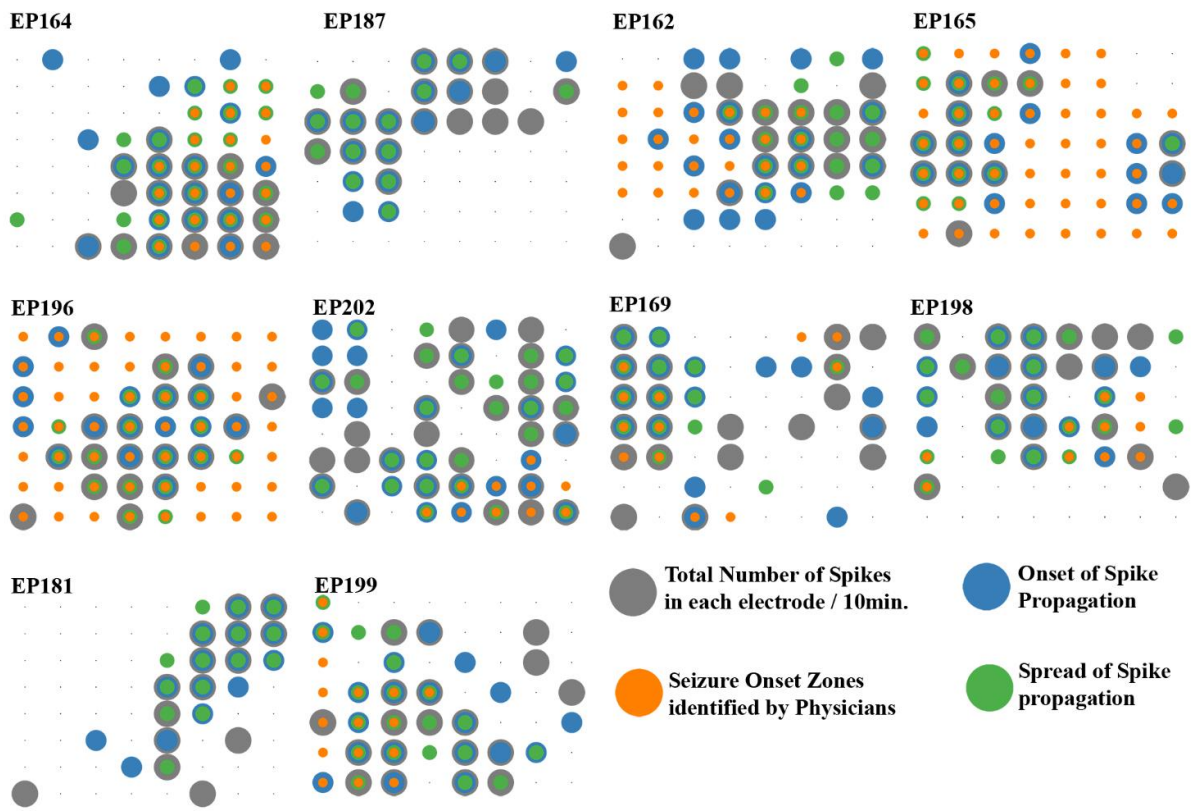


Figure 2.7. Spike and seizure onset patterns are not clearly interrelated and highly variable. We found no clear relationships between seizure onset zones identified within the selected electrode grid location and the spike occurrence, onset, and spread for all 10 patients. Note some patients who had infantile spasms had widespread ictal onset areas (patients EP164, EP165 and EP196). The size of each circle corresponds to the number of events at each brain location.

Interictal spikes are known to be highly associated with the epileptic state (Rodin et al. 2009; K. J. Staley and Dudek 2006) and are thought to result from synchronous cortical hyper-excitation of neural assemblies (Pillai and Sperling 2006). Previous studies have found that spikes have consistent frequencies and locations for each patient's interictal spike network and interictal spikes have been used to confirm the clinical diagnosis of epilepsy and to assist in the planning of drug management and epilepsy surgery (Pillai and Sperling 2006; Rodin et al. 2009). The spatially conserved pattern of spike propagation within each

patient signifies an invariability of the epileptic network over time. This suggests that once the wiring of neurons turns pathologic, the underlying network of interictal epileptic activity remains quite consistent.

A major question in epilepsy is whether interictal spikes are simply singlet spikes from a repetitively spiking seizure focus or represent an entirely different network. Previous research has suggested that, interictal spikes proceed the development of seizures, but when increased, correlate with spontaneous seizure events (White et al. 2010). It might therefore be possible to predict seizure onset regions based on occurrence of interictal spiking. However, there is widely discordant data for this hypothesis as it is well known that regions of high interictal spiking are not always seizure onset regions (J. Jacobs et al. 2008; Hufnagel et al. 2000; Marsh et al. 2010; Asano et al. 2004). There is conflicting data to support the removal of high spiking regions for a positive surgical outcome (Alarcon et al. 1997; Mégevand et al. 2014; Bautista et al. 1999; Asano et al. 2009). An important new observation from our study that may help resolve this discordance is that most regions with the highest interictal spiking frequency are not areas of spike onset, but areas that receive the spread of spikes.

All of these findings taken together favor the hypothesis that interictal spiking and seizure networks are distinct with different mechanisms of origin (Karoly et al. 2016). Surprisingly, except in one patient, we did not find a tangible relationship between spike onset and seizure onset. However, in the present study we did not use data from all brain regions covered by electrodes that could also be involved, nor did we focus on less frequent spiking regions in our dDTF analysis that focuses on the most common patterns of spread. Clearly, more research will be needed to explore the complex relationships between the interictal spike and seizure networks. Further studies will need to look at not only the spatial, but also the temporal relationships between interictal spike onset regions and seizure onset regions.

Another physiological aspect of epilepsy that has gained significant interest is in the area of HFOs. Some have found HFOs to highly correlate with seizure onset regions (Ochi et al. 2007; Jirsch et al. 2006; Modur and Miocinovic 2015; Salami et al. 2014; J. Jacobs et al. 2008). We looked at the propagation patterns embedded within interictal spikes and found that all frequencies, from lower frequency bands to HFOs propagate in a similar fashion. This may not be too surprising as it has previously been shown that

high frequency oscillations are often coexistent with interictal spikes (J. Jacobs et al. 2016, 2008; Rodin et al. 2009) and in the present study we focused entirely on interictal spiking.

By co-registering electrode locations with 3D MRI reconstructions, we examined the spatial aspects of spike propagation with respect to cortical structures. We found that the distance interictal spikes propagate is generally quite short, most often to adjacent electrodes, spikes can also traverse larger distances, likely through subcortical pathways, but the chances are few. Perhaps the most salient observation was that the central sulcus acts as a significant anatomic barrier to spike propagation in all patients we examined. The central sulcus divides primary sensory from motor cortex and is one of the deepest sulci in the brain that has been extensively studied for its functional localization and cortical plasticity. Identifying the location of the central sulcus is critical in surgical planning to reduce unwanted motor and sensory deficits (Towle et al. 2003). Previous studies have found that spikes originating from sulcal and gyral cortices on either side of central sulcus propagate across central sulcus (Jung, Kim, and Kim 2003). In contrast, when looking at all spiking events statistically, we observed that the central sulcus is a strong barrier to the spread of spikes. A recent study on human epileptic tissues that defined tissue markers of spiking found that molecular markers of epileptic activity in the MAPK/CREB pathway also failed to cross deep gyri, suggesting an underlying molecular and cytoarchitectonic underpinning that creates anatomical barriers across the cortex (Beaumont et al. 2012). Although from the current study it is difficult to point out the exact mechanism of how central sulcus acts as a barrier, a probable reason might be the large cortical surface coverage of the deep sulci and thinner cortex. More studies will be needed to connect structural and functional information together using a variety of connectivity measures including cortico-cortical evoked potentials or fiber tractography. This will allow further exploration of the effects of deeper sulci and other anatomical abnormalities on spike propagation networks across different brain regions. Because our study only involved surface grid electrodes, examination of spike propagation patterns from patients with stereo EEG could also help in this endeavor. Finally, propagation patterns may be age dependent and examining patients within different age groups would be helpful in learning how these networks may change as a function of brain development.

Several signal analyses tools have been proposed to quantify and understand interictal spike propagations. Granger causality based functional measures (Granger 1969), such as direct transfer function (DTF) (Bressler and Seth 2011) and partial direct coherence (PDC) (Baccalá and Sameshima 2001), evaluate the causal flow of information between signals in a multivariate environment. They provide statistical estimates of connection strength along with the direction that information flows. Since these evaluations compute the causality based on phase differences, they are robust to volume conduction as compared to other bivariate analysis. With simulated and experimental data, it has been shown that an enhancement of the DTF algorithm, direct DTF (dDTF), is more efficient in identifying causal connections (statistically) with fewer false detections. It also has a lower fictitious causal density and high spectral selectivity (Fasoula, Attal, and Schwartz 2013; Laura Astolfi et al. 2007; L Astolfi et al. 2005; Bressler and Seth 2011). Such approaches enable robust understanding of path and timing of network signal propagations. More recently, the direct-Directed dDTF has been successfully implemented in previous studies evaluating seizure propagation and epileptic source localization (Hur and Kim 2015; M. Kamiński et al. 2001; Anna Korzeniewska et al. 2008; Wilke et al. 2010).

The clinical implications for this work are still not fully developed. Although there are several limitations in the current study, and primarily we focused on evaluating the interictal spike propagation patterns, taken together our findings suggest that interictal spikes and seizures develop nearby, but from different networks. Whether removal of spike onset regions would produce a better surgical outcome remains an open question not answerable by our current retrospective data. However, application of this analysis prospectively could allow a greater understanding on whether disrupting or removing interictal spiking networks on surgical outcome.

III. EPILEPTIC SPIKE FUNCTIONAL NETWORKS BEST PREDICT SEIZURE ONSET ZONES

This chapter has been adapted from the following manuscript publication:

Maharathi, Biswajit, Jeffrey A. Loeb, and James Patton. "Epileptic spike functional networks best predict seizure onset zones." In 2019 9th International IEEE/EMBS Conference on Neural Engineering (NER), pp. 895-898. IEEE, 2019.

3.1. Introduction

Epilepsy is a severe neurological disease affecting 65 million people word wide. Most of these patients can control the disease with regular medication. However, for majority drug resistant cases, surgical intervention is one of best alternative. A key challenge in such cases is to find the seizure onset zones (SOZ), specifically when the seizure itself is a very rare event. There has been substantial research in identifying the SOZ with limited successful outcome.

In such cases, interictal (electrical recording collected in between two consecutive seizures) electrical information is an essential component. Past and recent studies have explored the potential use of interictal spikes (spike-slow wave complexes found during the interictal period) and high frequency oscillations (HFO, time-voltage segments in EEG where the power in the frequency band ~80-250Hz exceeds a predefined threshold) as a way to identify seizure onset zones. However, the relationship between interictal electrical information and seizure onset zones is not well understood.

We implemented a unique approach to evaluate the relationship between the interictal ECoG pattern and SOZ using a causal network. We implemented a Granger causality base network evaluation algorithm direct directed transfer function (dDTF) to estimate the functional network of the electrocorticography (ECoG, electrical signal collected from cortical surface of the brain) following two different approaches; first identifies interictal spikes and then building their network and second, taking the entire ECoG information and evaluating the causal functional network. We further calculated different properties of this directed network to find a potential relationship between the interictal functional network and SOZ. Below is comprehensive explanation of the graph properties we used.

1. Page rank: Assigns the weight of the node by measuring the relative importance of the node within the set of nodes.
2. Betweenness: Measures the importance of a node by calculating relatively how many times the shortest path between two nodes in a set of nodes pass through the node under consideration. We calculated the betweenness measure using different cost functions such as (1) betweenness with reciprocal of count of connection between nodes as cost function, (2) betweenness2 with geodesic distance between nodes as the cost function and (3) betweenness3 with (geodesic distance/ count of connections between the same nodes) as the cost function.
3. Indegree: Number of incoming edges to each node.
4. Outdegree: Number of outgoing edges from each node.
5. Hub and authority: These are two linked centrality measures where hub in general means the node that has links that greatly exceeds the average number of links in a directed graph. In Kleinberg's centrality measure, a hub is a node connected to authorities and a node is a authority if is linked to hubs (Kleinberg 1999).

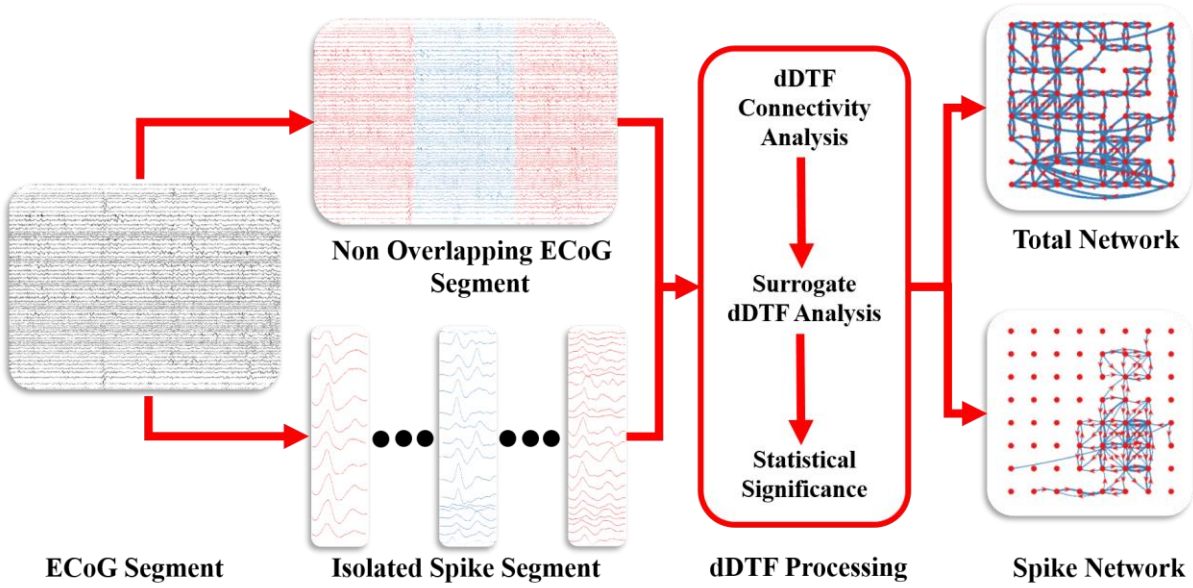


Figure 3.1. A simple schematic of the computational processing steps for both total and spike propagation.

Our goal here was to evaluate the different network centrality measure of the total functional network and the spike functional network in interictal ECoG and establish a relationship of these properties with SOZ in terms of predictability of SOZ.

3.2. Methods

We randomly selected 8 pediatric epileptic patients (4F / 4M, median age: 3 years) with drug resistant focal seizures, under an approved protocol by University of Illinois at Chicago. All patients underwent surgical subdural electrode implantation for long term recording. The electrocorticography (ECoG) recordings were obtained using a 124 Stellate Digital recording system with 1000 Hz sampling rate from subdural electrodes (4mm diameter, 10mm spaced apart). For current study, in each patient, we selected a set of 64 electrodes (8 X 8 grid), containing a subset of seizure onset zone (SOZ) identified by epileptologists.

The causal propagation was evaluated following two different approaches. In the first approach, we took the entire 64 channel ECoG and evaluated the functional network of consecutive 10 second long ECoG segment with zero overlap, using direct directed transfer function (dDTF) at different frequency bands (delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), gamma (30-50 Hz) and high frequency oscillations (HFO, 80-250 Hz)) (Biswajit Maharathi, Loeb, and Patton 2016). In the second approach, we identified interictal spikes (epileptic spike slow wave complex that occur in between two consecutive seizure episodes) using an robust existing algorithm (Daniel Tice Barkmeier 2010), and isolated the signal when at least two spikes appear in synchrony (if the peaks of a set of spikes appear within 100 millisecond time) for the selected electrode grid. Then these synchronous spike segments were processed through dDTF for causality estimations for the above mentioned frequency bands(Biswajit Maharathi et al. 2018). A phase randomized surrogate data validation method was implemented to validate the measured network in each case.

After functional network evaluation, different graph properties (page rank, betweenness, in degree, out degree, hub and authority) were evaluated. Further, each electrode position was ranked based on the numerical value of each of the previously evaluated properties of the graphs. We implemented a thresholding approach (0 to 100 with an increment of 5% at each step) to compare the top ranked electrode positions against physician marked seizure onset zones (SOZ) for each patient. For the comparative analysis, we used individual data points and the area under the receiver operator characteristic curve (ROC plotted True

positive rate on Y-axis vs. False positive rate on X-axis). Wilcoxon signed rank test was implemented for significance testing between different properties and other evaluations as well.

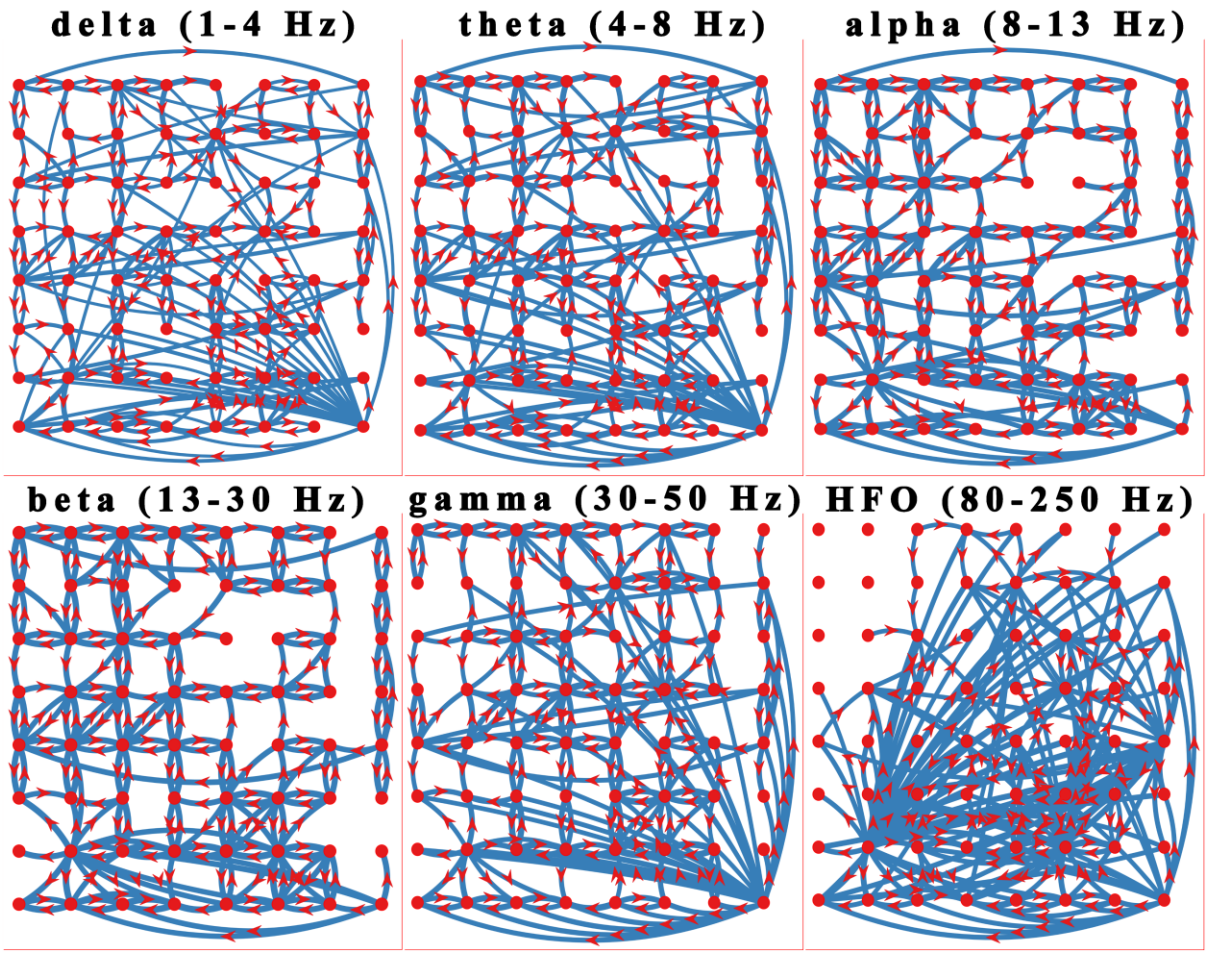


Figure 3.2A. Total propagation network for a patient at different frequency bands. Only top 5% propagations are presented here for a clear visualization. The red dots represent the electrode locations. The blue lines represent the connection between a pair of electrodes with thickness of line representing the propagation counts. The red arrow mark shows the direction.

3.3. Results

We analyzed the interictal total propagation and spike propagation in 8 epileptic pediatric patients admitted for epilepsy surgery. The goal of this study was to evaluate how accurately interictal functional network of brain helps in predicting the seizure onset zones. For a comparative analysis, we evaluated the performance of different graph parameters (page rank, betweenness, in degree, out degree, hub and

authority) at different ECoG frequency bands for both total and spike propagation. Using this comparison, we asked specific question, (1) does spike propagation better predicts the seizure onset zones, (2) is there any specific frequency band that best predicts the SOZ, (3) is there any specific graph property or centrality measure that has better predictability and (4) is there any gold standard of thresholding these parameters to obtain the best prediction of seizure onset zones.

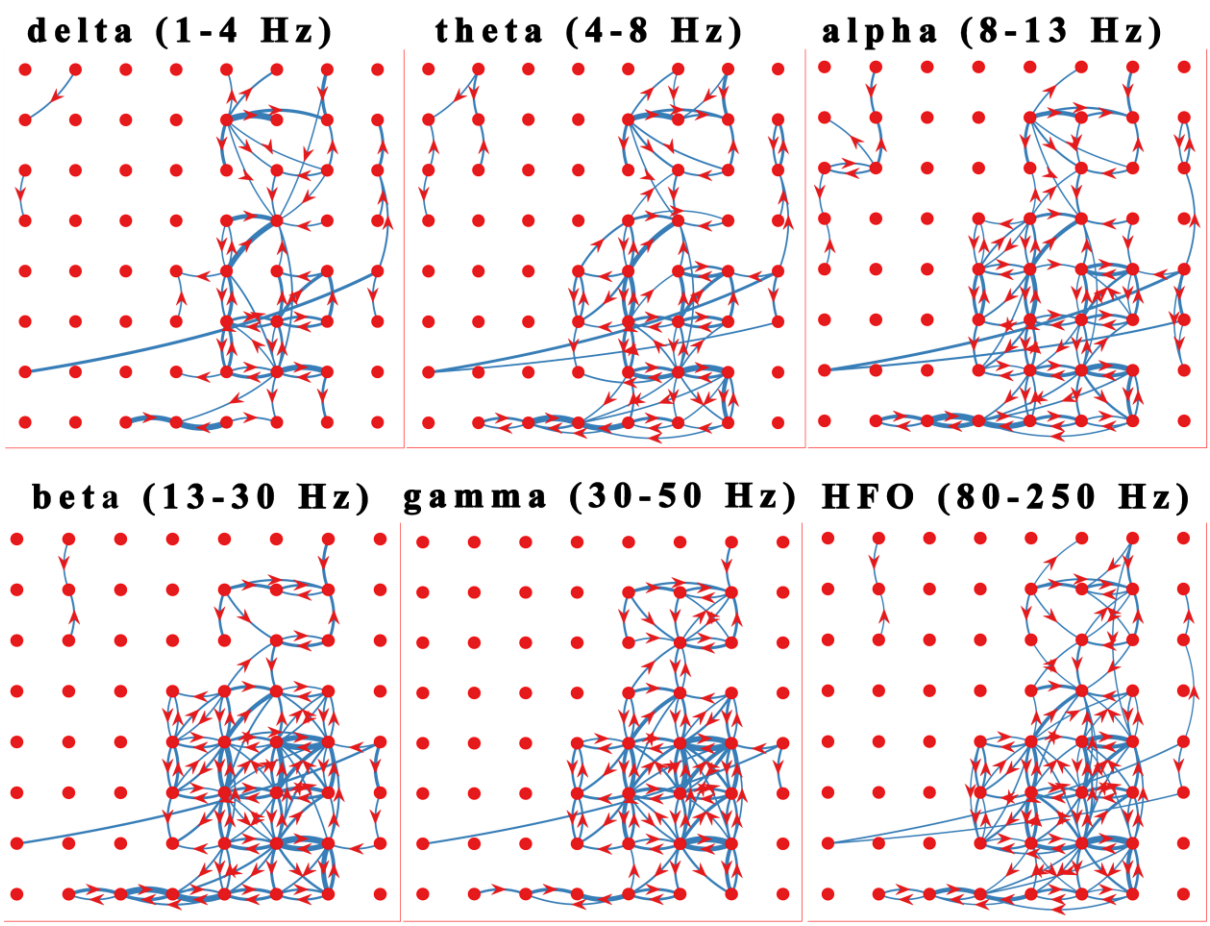


Figure 3.2B. Spike propagation network for the patient shown in fig.3.2A at different frequency bands. While this process is thresholded in the same way as Figure 3.2A, it yields differing results.

3.3.1. Interictal spike propagation is a better predictor of seizure onset zones

We comparatively evaluated the ROC curve and area under each ROC curve for different graph properties. The ROC curve for spike functional network properties, at all frequency bands were significantly performed better in SOZ prediction compared to the respective properties in total functional network ($p<0.05$)

with very few exceptions, where either the ROC curve was below the random guess line or the frequency band was HFO. Also the area under the curve in spike propagation network was comparatively higher than the total propagation network ($p < 0.05$) (Fig. 3.3A & 3.3B) concluding that the spike propagation network properties are better predictors of seizure onset zones compared to total propagation network.

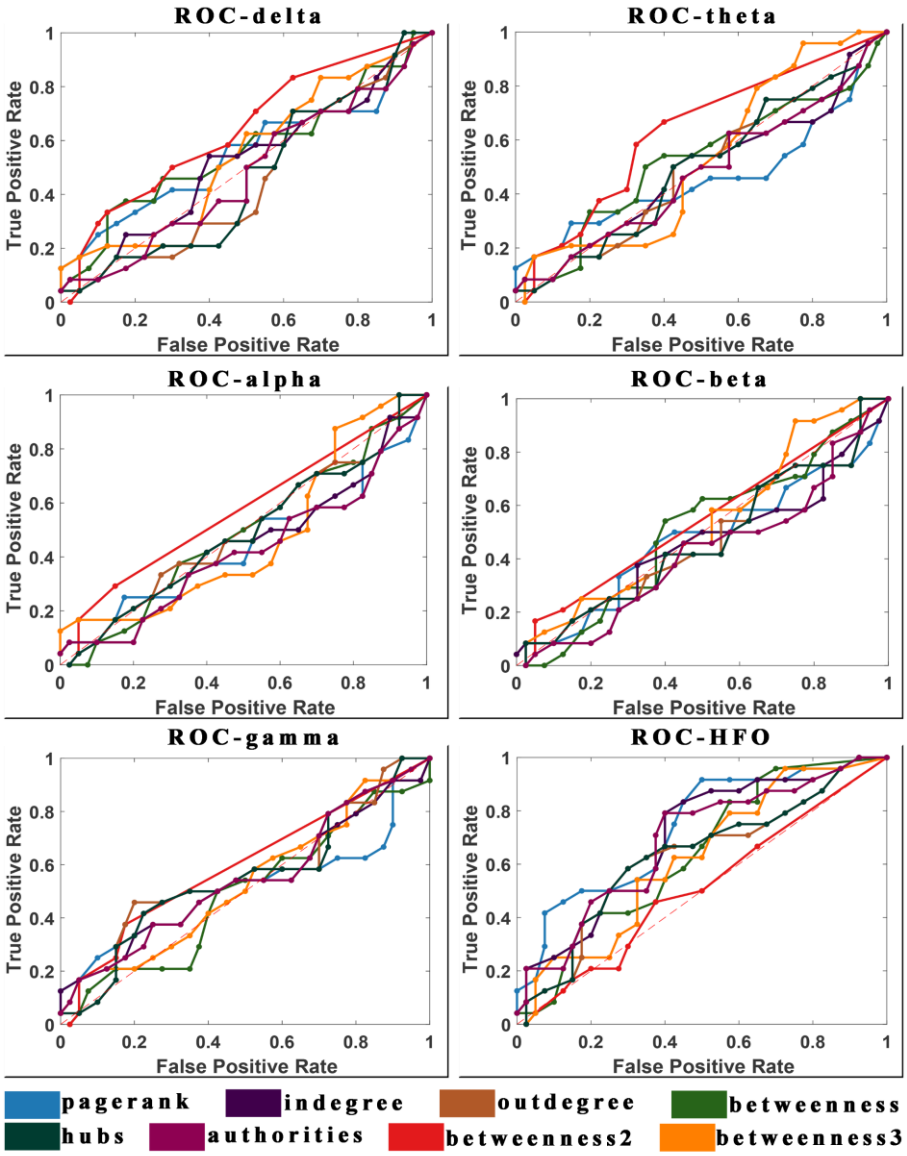


Figure 3.3A. ROC curve for each ECoG band and all graph properties in total propagation network shown in fig. 3.2A.

3.3.2. In total propagation, the best predictions come from the HFO band

In total propagation, since HFO network was frequently observed to be a better predictor of SOZ compared to other bands in total propagation (Fig. 3.3A), we further evaluated whether the difference is significant. We observed that in 6 out of 8 patients, HFO was significantly better in predicting SOZ compared to other frequency bands (ROC curve comparison: $p < 0.05$, AUC comparison $p < 0.05$).

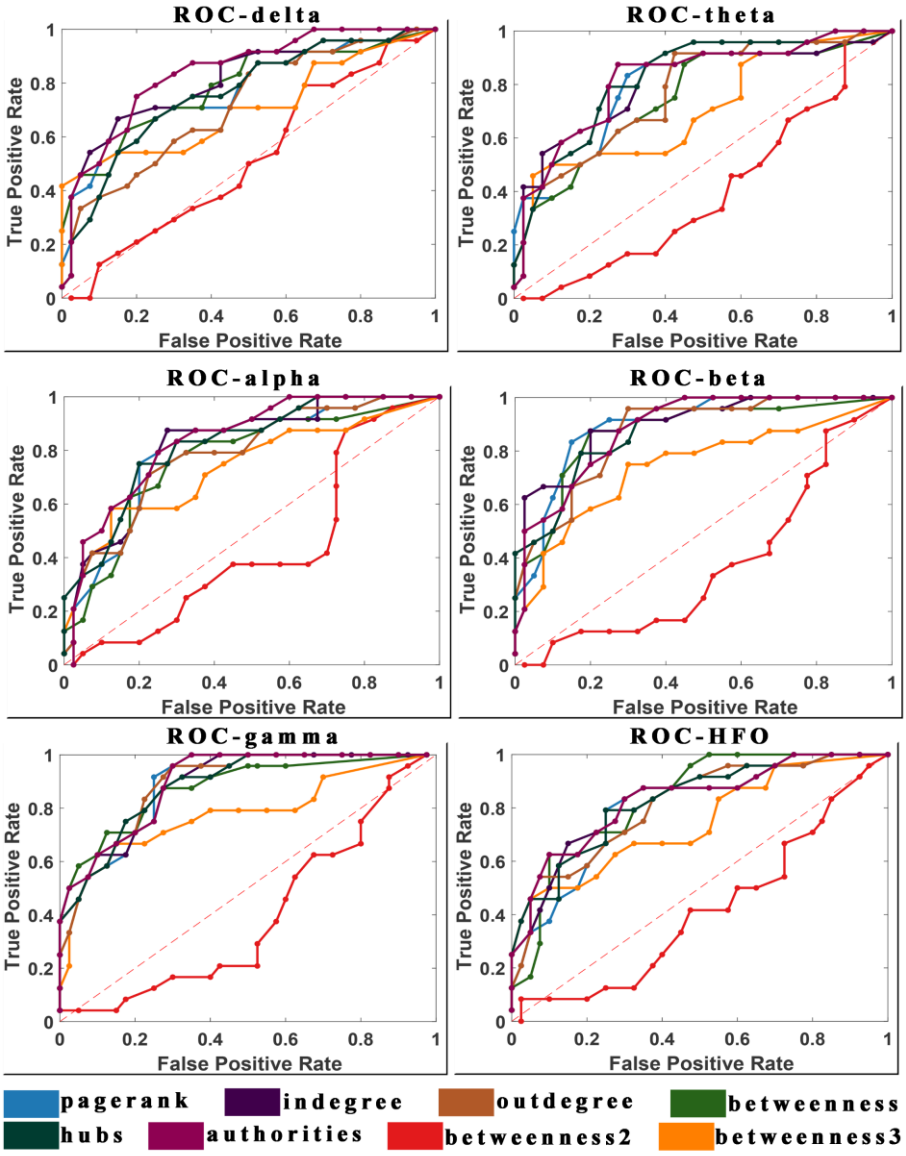


Figure 3.3B. ROC curve for each ECoG band and all graph properties in spike propagation network shown in fig. 3.2B.

3.3.3. Spike propagation network in all frequency bands predicts SOZ in a similar way

In spike propagation network, all frequency bands predicted SOZ with very similar accuracy ($p<0.05$) with exception of beta and HFO band producing the best accuracy.

3.3.4. Different graph properties predict SOZ differently depending on frequency band and patients

We dived into more detailed analysis on how well the different graph measures predicted SOZ at different frequency bands in spike functional network. While often, there was no significant difference between frequency bands in predicting SOZ, there were few exceptions. In four patients, beta band outperformed other frequency bands (AUC comparison, $p<0.05$).

Out of all tested properties, PageRank was frequently the best property predicting SOZ ($p<0.05$, best predictor of SOZ in 4 out of 8 patients). Other properties such as authority, indegree and hub were also alternative graph properties good at predicting SOZ ($p<0.05$). Although the betweenness centrality was a good predictor, it performed poorly in most of the patients.

3.3.5. A lower threshold value works best for seizure onset prediction

We calculated the distance of each data point on ROC from [0, 1] (top left corner of ROC curve) to find the threshold which is most accurate in predicting the SOZ. The optimum threshold value was 55% ± 13 (median ± SD) except one patient where the median threshold value was 15%.

3.4. Discussion

Interictal spikes are the signature electrophysiological biomarker of epilepsy. These events have been associated with seizure onset zones frequently (de Curtis and Avanzini 2001). Subsequently there have been an increasing number of studies that focus on functional networks using the entire ECoG signal including very high frequency bands to establish a relationship between HFOs and SOZs (Wilke et al. 2010; J. Jacobs et al. 2008). When we took this unique approach by first identifying epileptic spikes rather than the more traditional approach of including the entire EEG segment in our analysis, we show significant superiority in detecting SOZs.

This suggests that not all network events are pathologic, and we need to focus more on aberrant electrical activities to best discern pathologic networks. However, looking at the spikes is only possible when they are

abundantly available and represent themselves in a synchronous manner as is commonly seen on intracranial recordings. In cases, where spikes are not present, additional parameters may be needed to identify the pathologic network using the entire ECoG.

Although we discovered that, the HFO network in the total functional network was quite effective in most patients predicting the SOZ, it was still not as accurate as spike network. Apart from HFO, we also observed that in spike network in beta band was also effective in predicting the SOZ accurately, however further research is necessary with a larger patient sample to establish the relationship between beta band activity with SOZ.

Previous studies have established that the betweenness centrality when evaluated using seizure data or interictal ECoG, has been a good predictor of SOZ (Wilke, Worrell, and He 2011). However in the current study, we discovered that there are other centrality measures of graph which significantly better in predicting seizure onset zones compared to betweenness measure. We also implemented page rank algorithm on the functional total and spike network and discovered that this is one of the best predictors of seizure onset zones using the network activity.

One of the patients had all electrodes marked as seizure onset zones (prevalence = 100%), in which case there was no false positive and high sensitivity was achieved with very thresholds with deterministic specificity. In such cases, there needs to be an alternative robust parameter to estimate the efficacy of network in detecting the seizure onset zones.

While looking for the optimum thresholding value, we found that high thresholding was not a very effective measure to detect SOZ, in fact for most patients, across all frequency bands and different parameters, lower threshold as close as ~50% worked much better in predicting SOZ. In one of the patients where prevalence was ~96%, we observed that the betweenness was an accurate predictor and the threshold required was as low as 15%. The curious question of whether high prevalence has any dependency of threshold or other graph measures is case requiring further research.

3.5. Conclusion

The key takeaway from the current work is that granger causality measure of appropriate dataset using dDTF when combined with different graph centrality measures proves to be an effective tool in predicting the

seizure onset zones. We discovered that use of properties of isolated synchronous interictal spike functional network is a better predictor of seizure onset zones compared to the total brain network, where different frequency bands played a little role. Further work in this direction has the potential in assisting physicians taking appropriate measures in determining the seizure onset zones as well as other focal activity accurately during pre-surgical decisions and can enhance our understanding of basic brain functionality and connectivity.

IV. CENTRAL SULCUS IS A BARRIER TO CAUSAL PROPAGATION IN EPILEPTIC NETWORKS

This chapter has been adapted from the following manuscript publication:

Maharathi, Biswajit, Jeffrey A. Loeb, and James Patton. "Central sulcus is a barrier to causal propagation in epileptic networks." In 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC), pp. 2555-2559. IEEE, 2019.

4.1. Introduction

Brain functional networks are dynamic in nature representing the spontaneous interaction of different brain regions. Previous research on structural connectivity and functional brain networks suggest that although these functional dynamic networks produce distinct graphs of interactions during different task specific activity, they are not entirely a product of it. The structural arrangements of the brain which are quite resilient in nature certainly alter the spontaneity of such networks (Park and Friston 2013). These structural arrangements also mediate both local and global network manifestations. However, such nature of the structural connections is not fully understood. What is needed is an approach that evaluates the functional connectivity while also considering the underlying structure.

Bivariate algorithms such as correlation, coherence and partial coherence based studies have revealed the pairwise functional connections [1], and more recently multivariate algorithms such as Direct Transfer Function and Partial Direct Coherence have used parametric modelling to robustly identify causal propagations. We prefer Granger causality-based direct directed transfer function (dDTF) to evaluate the functional causal networks. This method has been used extensively and proven to identify the most likely direct connections in a multivariate environment (Fasoula, Attal, and Schwartz 2013; Anna Korzeniewska et al. 2008; Hur and Kim 2015; Laura Astolfi et al. 2007; Bianchi et al. 2013; Biswajit Maharathi et al. 2018). Using these functional networks, we have understood that the pathologic functional networks are very consistent (Biswajit Maharathi et al. 2018; Biswajit Maharathi, Loeb, and Patton 2016).

Structure influences functional propagation, irrespective of disease, time or frequency band (Biswajit Maharathi et al. 2018; Biswajit Maharathi, Loeb, and Patton 2016; Park and Friston 2013).The above

evaluated network was then integrated with the brain topography calculated from the MRI imaging and further statistical methods were performed to establish the relationship between interictal spike-epoch propagation occurrence and geodesic distance(Biswajit Maharathi et al. 2018). We also observed that the large sulcal patterns such as the central sulcus acts as a barrier to the propagations in the interictal spike network (Biswajit Maharathi et al. 2018). Such variations in propagation with respect to brain topography are important, however they have not been extensively studied.

A critical aspect affecting these results may be what portions of the data recording has been used. Our interictal spikes causal network used a preselected subset of the time records that isolated the epochs of interictal spike propagation (Biswajit Maharathi et al. 2018). It may be important to compare the functional network arising from the entire interictal time record (full network), and whether this also is affected by such structural barriers. This may be further dependent on different frequency bands.

In this paper, our major focus was to evaluate (a) how often propagation events in full network occur between distant cortical regions compared to adjacent locations. Since Central sulcus is one of the largest sulci in the brain, it was our focus to understand its role as a barrier to functional network propagations, so we enquired (b) to what extent the central sulcus plays a role in restricting the information flow in the full pathologic network. We preferred to have the network evaluation in two different approaches. First, we considered to take the continuous non-overlapping ECoG segments and evaluate the network which we call full network. In the second approach we analyzed the isolated interictal spike network (spike network). Using both these networks, we asked the question (c) does propagation distance with respect to brain topography change differently in both these networks and does central sulcus play the same role for both these networks when evaluated at different frequency bands. Such specific understanding of the complex brain structural and functional network would reveal fundamental operations of the brain and help explore pathological networks and task specific network interactions in an improved manner.

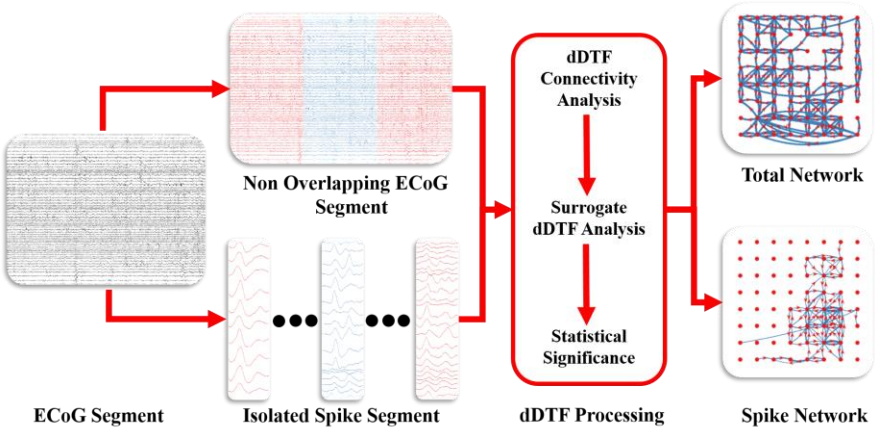
4.2. Methods

4.2.1. Data Collection

We selected 7 epileptic patients (4 Female/ 3 Male, median age: 3 years) who underwent two-stage surgery due to drug resistant epilepsy, under the approved protocol of University of Illinois at Chicago. All

seven patients underwent long term video-EEG monitoring with subdural electrodes (4mm diameter, spaced 10mm apart). Three 10-minute electrocorticography (ECoG) recordings were extracted from the EEG database recorded with 124 electrode stellate digital recording system with 1000 Hz sampling rate. For the current study we selected a set of 64 electrodes (8X8 frontal temporal grid) containing the central sulcus (the central sulcus divides the grid with approximately equal number of electrodes on either sides). The quality of the dataset along with all the evaluations were verified by a trained epileptologists.

a. Signal processing schematics:



b. Image analysis schematics:

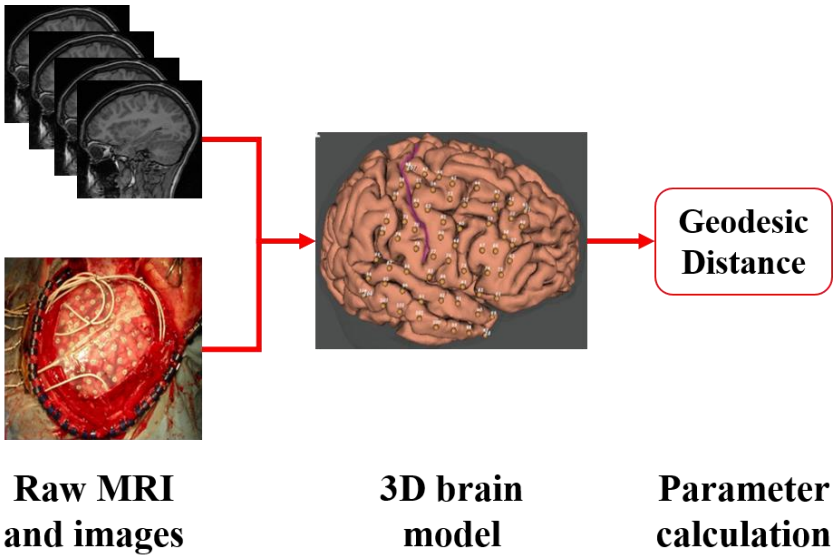


Figure 4.1. A simple schematic representation of the signal and image processing steps. (a) Explains the stepwise processing of full and spike signal and (b) shows the stepwise processing of the MRI scans to get the different parameters.

4.2.2. Signal Analysis

The causal propagation network was evaluated following two different approaches. In the first approach, we took entire 64 grid electrodes ECoG information. Following a windowing approach, we evaluated ECoG with 10s continuous non-overlapping time segments of the full dataset. In the second approach, like in (Biswajit Maharathi et al. 2018), we first marked the interictal spikes and isolated time segments that contained synchronous multiple interictal spike events with spike peak within 100 milliseconds time period. Further we extracted approximately 350ms time segments for each spike within the spike synchrony. For the causality evaluation we used direct directed transfer function (dDTF) (Biswajit Maharathi et al. 2018; Biswajit Maharathi, Loeb, and Patton 2016). Briefly, we performed Phillips–Perron test to check the stationary nature of the signal. We then fit each epoch of the data to a multivariate autoregressive model using modified covariance method. The model fit order was determined using Akaike information criterion where the maximum order was fixed to 20th order. Further using this model, the dDTF values for each pair of electrode information was calculated. Both the approaches were verified using a phase randomized surrogate data method. Here we created 100 copies of the surrogate data and compared it with the original output. If the area under the original dDTF values for a pair of electrode was greater than the 95th percentile of the surrogate dataset dDTF values, then the propagation between the same pair of electrodes, we accepted that propagation as a real propagation.

Both the above mentioned approaches were evaluated at different frequency bands such as delta (1-4Hz), theta (4-8Hz), alpha (8-13Hz), beta (13-30Hz), gamma (30-50Hz) and high frequency oscillation (HFO, 80-250Hz). Once the functional network was evaluated it was further used along with the imaging information to analyze the effect of brain topography on functional networks.

4.2.3. Image Analysis

We obtained the MRI images for each patient and constructed the 3D models using freesurfer. We further co-registered the electrode positions using CT images and cross verified with intra-operative images taken during grid removal to ensure that they did not move. We then marked the central sulcus and computed the geodesic distance for each pair of electrodes within the considered grid. An outline of the methods is given in Fig.4.1.

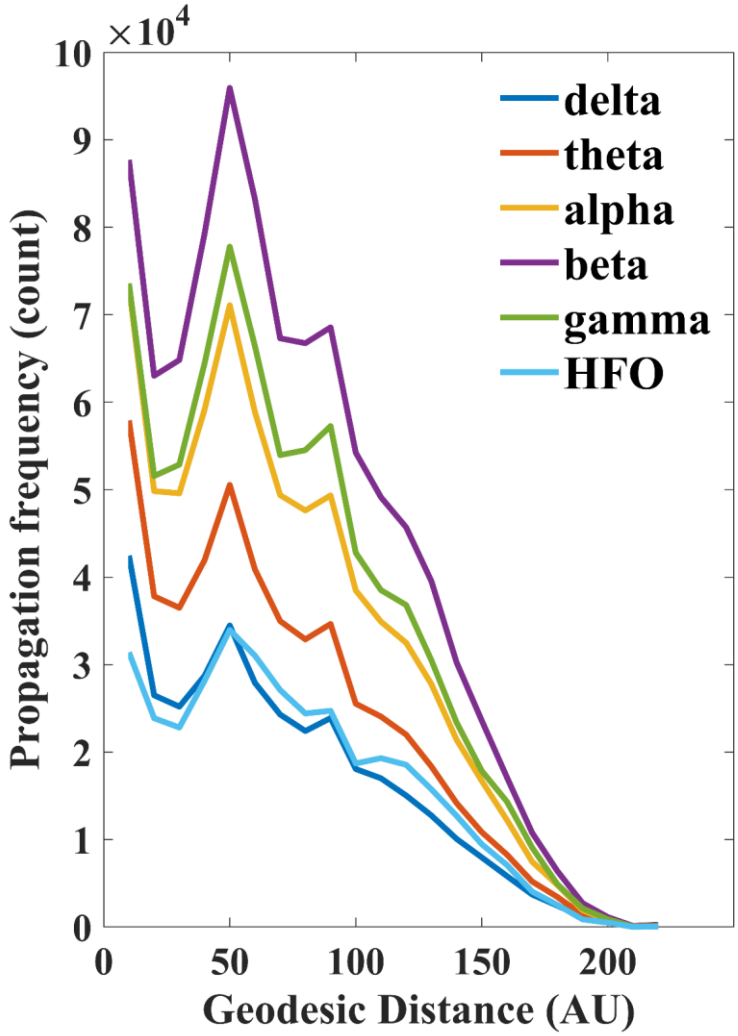


Figure 4.2. Propagations in full network travel to adjacent locations as well as distant cortical regions but less frequently. The x-axis represents the geodesic distance which quite translates to centimeter scale. The y-axis represents the total count of propagations combined for 7 patients. While until 100 geodesic distance (AU), the propagation count remains high, it reduces by 50% at that distance and decreases drastically with respect to increasing geodesic distance.

4.3. Results

We were able to analyze interictal propagation networks of 7 epileptic patients using our two sets of extracted data: one where epochs of inter-ictal spike propagations were isolated in time (spike epochs) and one where 10-second windowed segments of the entire dataset were used (full dataset). The goal of the research was to evaluate the relationship between functional networks and the topography of the brain. For

this analysis we evaluated both the networks across a range of frequency bands. We demarcated the central sulcus and computed the geodesic distance for each pair of electrodes within the considered grid of electrodes. Using this multimodal dataset, we evaluated a set of specific questions: (1) Do propagations in full network travel distant electrodes, (2) does the central sulcus restrict the propagations in full network, and (3) do anatomical structures have a similar effect on the full network as they have on the spike network.

4.3.1. Propagations in the full network travel adjacent locations as well as distant cortical regions

Propagations in the full network travel to both adjacent electrode positions as well as to distant locations, however after a certain distance, sudden decrease of propagation count is observed (Fig. 4.2). We observed that the count of propagations becomes half after ~100 geodesic distance (AU) and after that the decrease is more sudden as observed in Fig. 4.2. Although the absolute count of propagation in each frequency band is different, the overall pattern of propagations corresponding to increasing geodesic distance remains quite consistent (mean correlation coefficient = 0.99, $p<0.005$) suggesting that propagation patterns behave in a similar fashion with respect to geodesic distance for all frequency bands.

4.3.2. Central sulcus restricts propagations in full network

We counted the number of propagations occurring on the same side of the central sulcus and compared it with the count of propagations crossing it. The propagation counts on the same side of the central sulcus (NoCross) and crossing the central sulcus (CrossCS) were normalized to the respective electrode counts on each side. We first hypothesized that the central sulcus has no effect on propagation where it was assumed that each electrode in either side of the central sulcus propagated to each electrode with equal probability for each epoch of data. Using this assumptions, we determined the number of probable propagations and calculated the proportion of propagations that would have remained on the same side of the central sulcus compared to the proportion of propagations crossing the central sulcus (Fig. 4.3a). We then compared these values with the actual propagation events observed in the full propagation network. In full propagation network we observed that in all patients, percentage of propagations crossing the central sulcus (~30 %) was significantly lower ($p<0.005$) compared to propagations on the same side of the central sulcus (~70 %) (Fig. 4.3b). We investigated similar behavior in all frequency bands and found that the percentage of propagations crossing the central sulcus did not change significantly (30%± 1.3, mean ±SD). However, these

values were significantly different (p<0.005, Two-sample Kolmogorov-Smirnov) from the null hypothesis values (47.7% ± 4.67 crossing CS) suggesting that the central sulcus truly restricts the propagation of events across different frequency bands. We further investigated whether the propagations that cross central sulcus is similarly affected by the geodesic distance compared to the propagations occurring on the same side of the central sulcus. Although we observed the relationship between propagation crossing central sulcus vs. distance has similar nature as the propagations occurring on the same side of the sulcus (Fig. 4.4c), there was a distinct delay in terms of geodesic distance (~50 AU distance).

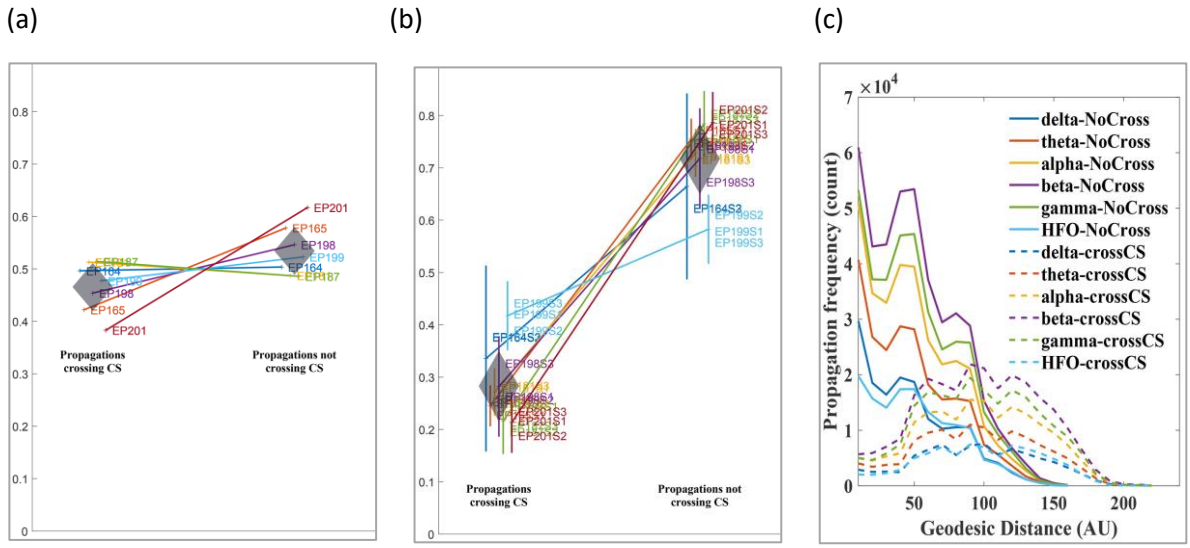


Figure 4.3. Central sulcus restricts the propagation of events in full network. This figure compares propagation count crossing the central sulcus versus the propagation count staying on the same side of the sulcus in (a) the null hypothesis case where the assumption was that each electrode propagates to each other electrode and there is structural barrier to any propagation events and (b) the propagations found in Full network theta band. Solid lines represent the difference between propagations crossing the CS vs not crossing with $p < 0.05$. Each vertical line with three points on it represents one patient with results from three 10-minute ECoG files. The height of the line is the variance between three data points. The width of the diamond shape represents the variance of mean of number of propagations crossing or not crossing the CS across all patients and the height of the diamond shape represents the variance of variance of propagation crossing or not crossing the CS across all patients. (c) Shows the cumulative count of propagations in all patients vs. geodesic distance on x-axis. The solid lines represent the propagations on the same side of the central sulcus and the dashed lines are for propagations crossing the central sulcus.

4.3.3. Brain topography affects full network differently than spike network

In our previous work we have discovered that propagations in spike networks mostly travel to adjacent locations and count of propagations is dramatically reduced with increasing geodesic distance (Fig. 4.4b). While in full network, we observe that the propagations travel longer distance, in spike propagation comparatively the propagation mostly travel to adjacent electrode positions with shorter geodesic distance (Fig. 4.4).

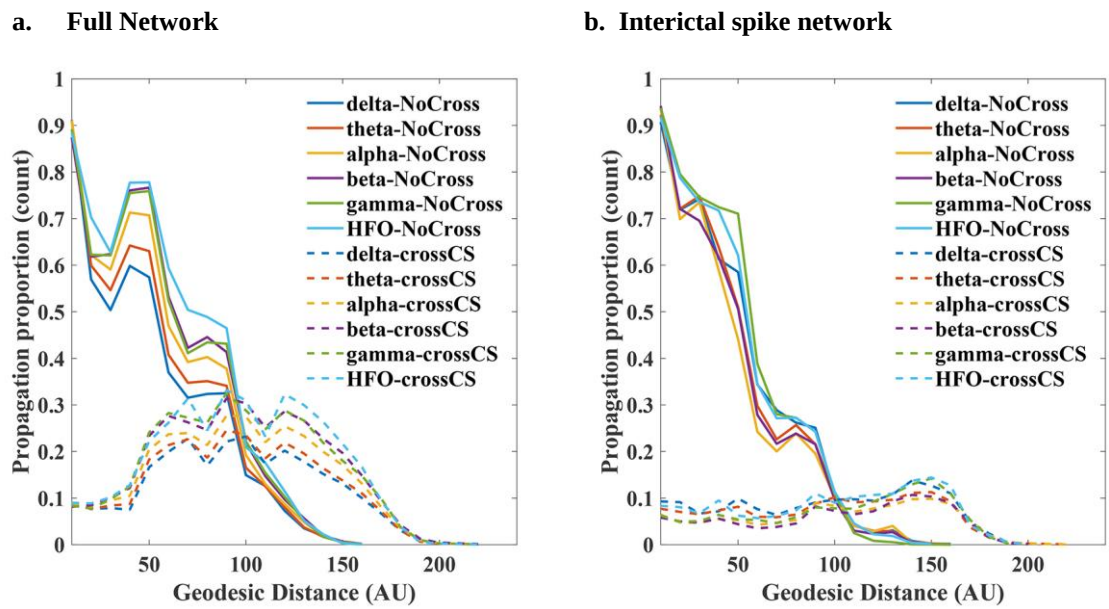


Figure 4.4. Comparative visualization of full and spike propagation occurrence on y axis vs geodesic distance on x-axis. Propagations in spike network travel mostly to adjacent locations. While until 50 geodesic distance (AU), the propagation count remains high, it decreases drastically with respect to increasing geodesic distance at all frequency bands. Although the absolute count of propagations remains different at different frequency bands, the overall pattern remains highly correlated. In both the propagation networks, while there are three distinct peaks observed, the transitions are more distinct in spike propagation with longer geodesic distance.

Moreover, the central sulcus also affects both networks differently. While in full propagation network approximately 30% of the propagations cross the central sulcus, in the case of spike propagation the number reduces to 21%. In spike propagation only 21% of the propagation travel across the central sulcus while the remaining 79% propagate on the same side of the central sulcus. This observation on both functional networks remain very consistent across all frequency bands.

We also observed that the propagations crossing the central sulcus has different relationship with geodesic distance in both full network and spike network. While the distance delay in full network was

approximately 50 AU with consistent propagations till 150 AU, spike network had propagation observations vs geodesic distance for propagations crossing central sulcus differently. Although we still can observe three small peaks in the propagations crossing the central sulcus as compared to the propagations on the same side of the central sulcus, the propagation counts are pretty low, and at around 150 AU geodesic distance good number of propagations are observed.

4.4. Discussion

Understanding the functional network of the pathologic brain has drawn a lot of attention in recent years. Analysis of such networks has helped identifying the seizure onset zones (Bandt et al. 2014; Wilke et al. 2010), helped in exploring the interaction of interictal epileptic spikes (Biswajit Maharathi et al. 2018), and in general helped understand the dynamic function of the brain. However, such functional networks don't function independently. Even though the pathological conditions alter the brain networks, these changes are also affected by the brain topography.

In the current study, we observed that the propagations travel differently depending on the type of network. While in the spike network, these propagations travel mostly short distances, in the full network these propagations are observed to be travelling short to moderate distances (Fig. 4.4). However, one common observation in both the networks is that the propagations are observed to be frequently travelling to adjacent locations and shorter geodesic distance. This might suggest that often the neural excitation is sufficient to excite nearby cortical areas, and brain communicates in a cascading flow of information instead of direct information delivery with high excitatory potentials. We also investigated specific case of propagations vs geodesic distance in propagations crossing central sulcus verses propagations not crossing. In full propagation network, although the count of propagation decreases rapidly in case of propagations not crossing central sulcus (Fig. 4.4a), the drop in propagation count was different in propagations crossing the central sulcus (Fig. 4.4b). We observed a rapid rise in the count of propagations with geodesic distance around 50 AU, after which the count remains consistent till 150 AU and then falls rapidly. Such nature might be due to the large cortical folding of the central sulcus. The shorter distance propagations observed in this might be the edge cases where electrodes are closer to the regions where the central sulcus starts or ends. In such locations the sulcal folding decreases, reducing the distance between electrode pairs. This nature of

propagation was observed across all the frequencies that we have analyzed here. We also observed a similar behavior in spike propagation across different frequency bands, but the effect was rather more drastic.

We also observed that the central sulcus restricts the propagation of events in both networks, but differently. While 30% of the propagations cross the central sulcus in full propagation, only 21% of the propagations cross the central sulcus in spike propagation. The physiological explanation for such behaviors would be complex, however we understand few things. The spike propagation network is a subset of the full network, representing pathological epileptic activity of the brain. The full propagation might include other functional communications that are essential to the basic functioning of the brain, and hence have higher number of propagations in general as well as higher proportion of propagations crossing the central sulcus compared to spike propagation network. This result might also reflect on the compartmental structure of the brain where naturally the brain is trying to restrict the high pathological activity while maintaining the physiological stability. However, with this limited information, concluding is difficult and further research is necessary to understand the science behind such behavior.

Although the results in this study are significant, there are several limitations to this study if we are to draw a stronger conclusion and generalize the outcomes. For the current research, we only considered a limited set of electrodes with a small brain area coverage. A detailed whole brain analysis would provide more information on events on both ipsilateral and contralateral sulcal patterns. Moreover, we need to look at other sulcal and gyral patterns to understand the effect of topography. We also need to compare such pathological networks with normal healthy person's functional network. Although we have used very robust algorithms evaluating the direct causal network, it would be interesting to look at the comparative analysis of the direct and indirect propagation network along with integrating other brain imaging modalities.

4.5. Conclusion

The key takeaway from this study is that the propagations do not travel to distant locations in general whereas the spike propagations are mostly confined to adjacent locations. Secondly, anatomical structures like the central sulcus act as a strong barrier to propagation of events and such structures must be included while performing functional network studies.

V. HIGHLY CONSISTENT INTERICTAL SPIKE NETWORKS IN TEMPORAL LOBE EPILEPSY

5.1. Introduction

Temporal lobe epilepsy (TLE) is the most common type of drug-resistant epilepsy. Hippocampal sclerosis (HS), also known as mesial temporal sclerosis, is the most common pathologic substrate of TLE(Velasco et al. 2006),and is seen in about 70% of patients with drug-resistant TLE(Engel et al. 2012). TLE is often intractable and is one of the most common types of pharmacologically resistant epilepsy. Epilepsy surgery with removal of the epileptogenic zone can lead to seizure freedom in up to 89% of patients during the first 2-3 years of follow up(Salanova, Markand, and Worth 2002).

To achieve a good surgical outcome, precise location of the epileptogenic zone is critical. In many patients, this will be possible only with intracranial recordings. The most used methods for intracranial recordings are grids (with subdural electrodes) or depth electrodes (stereo EEG-SEEG). Both are often used for intractable cases where no definitive focus can be found with scalp electrodes(Bancaud et al. 1970).

Another less invasive approach is the insertion of foramen ovale (FO) electrodes for the assessment of mesial structures(Velasco et al. 2006; Nilsson et al. 2009). Intracranial FO electrodes can record epileptic interictal spikes (95% of spikes not observed on scalp EEG) and seizures in Alzheimer's disease which are often not observed on the scalp EEG(Lam et al. 2017). FO electrodes can also be useful in identifying focal seizure onset where scalp EEG is unable to detect these events(Velasco et al. 2006). Coupled with high resolution imaging including MRI, PET and SPECT, FO electrode data can help guide surgical or other invasive treatments(Beleza et al. 2010).

Growing evidence suggests that epilepsy is not simply a disease of individual neurons, but of abnormal electrical and anatomical networks in the interictal state that predisposes the brain to seizures. To date, interictal networks have been measured mostly through functional connectivity studies in temporal lobe epilepsy. Resting state MRI demonstrates disrupted connections in temporal lobe epilepsy(Waites et al. 2006) and lateralization of the hippocampal network helps identify epileptic foci(Tracy and Doucet 2015). Hippocampal networks have been associated with neurocognitive function(M. Holmes et al. 2014) with

increased hippocampal functional activity in temporal lobe epilepsy(Haneef et al. 2014) and decreased hippocampal and amygdalae connectivity in temporal lobe epilepsy(Pittau et al. 2012). While clearly demonstrating the existence of epileptic networks that can interfere with normal networks, functional imaging studies are mostly correlative and lack sufficient time resolution compared to EEG to produce a detailed electrical map of interictal networks.

Here we used a directed direct transfer function (dDTF) to measure the interictal spike networks from long-term FO EEG recordings on 10 consecutive patients combined with high resolution MRI. Interictal spike networks were highly reproducible across time and included all neurophysiological frequency bands. We found that interictal spike networks are unique for each patient and closely related to structural brain lesions and seizure onset zones and therefore could be of significant value for improving surgical and non-invasive treatments.

Table5.1. Patient clinical information (note: 5 and 10 are the same patient with two separate recordings).

Patient	Age (Years)	Sex	Age of Onset (Years)	MRI Image Findings	Seizure Onset
1	39	F	17	Tumor (teratoma) in left hippocampus	Left anterior temporal
2	44	M	10	Left hippocampal sclerosis	Left anterior temporal
3	34	M	20	Left temporal dysplasia	Left posterior temporal
4	45	F	06	Left hippocampal sclerosis	Bilateral independent temporal
5	52	M	27	Diffuse volume loss	None captured
6	55	M	20	Normal	None captured
7	21	M	14	Normal	Extra temporal
8	36	F	0.5	Normal	None captured
9	48	M	36	Left hippocampal atrophy	None captured
10	51	M	27	Diffuse volume loss	None captured

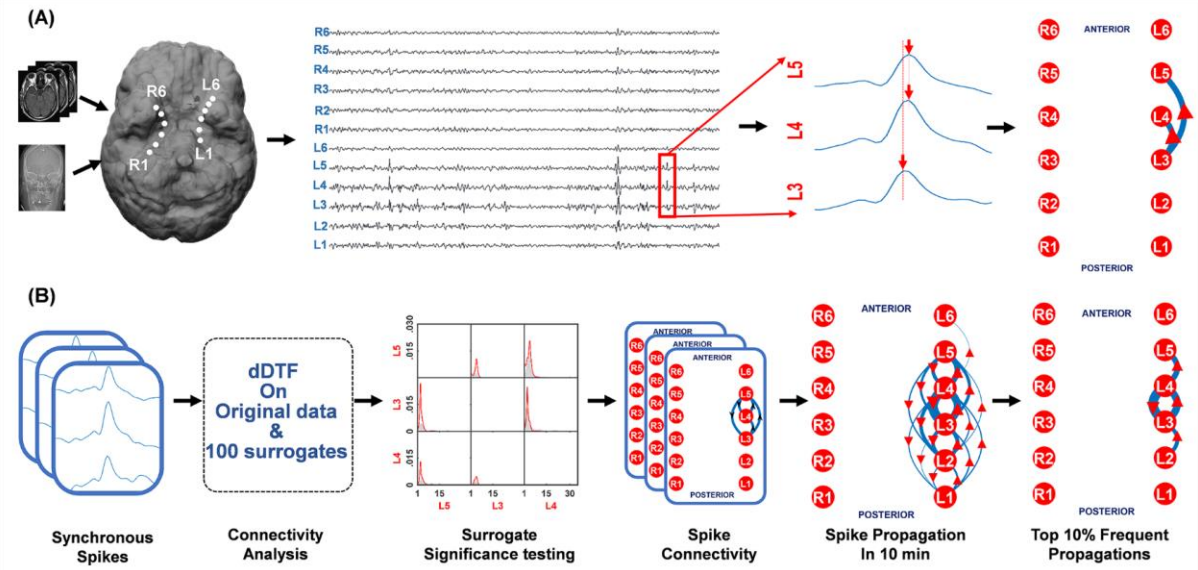


Figure 5.1. **Interictal spike propagation networks are measured using a direct directed transfer function (dDTF)**. (A)Using the MRI and CT scan, the electrodes placed through the foramen ovale are co-registered showing their proximity to specific mesial temporal structures. Spikes detected from the FO electrodes appear synchronous, but when closely examined have clear time delays such as between electrodes L3 and L4/L5. (B) dDTF was applied to a given 10-minute EEG segments after spikes were first marked using an automated spike detection algorithm. The detected synchronous appearing spike blocks of spikes were then extracted and processed through the dDTF based connectivity analysis. This function, that combines surrogate data analysis and statistical validation, provides a spike propagation network for each block of spikes, which is then further consolidated for 10 minutes of EEG. The top 10% of spike propagations are shown in the far right to create a simplified network for further analysis. In each schematic the thickness of the arrow indicates the frequency of a particular propagation pattern and the arrowhead indicates the direction of spread.

5.2. Methods

5.2.1. Patient Selection

The retrospective study was approved by the Institutional Review Board at University of Illinois at Chicago. We studied 10 consecutive FO patients who had undergone FO electrode placement along with scalp electrode placement as a part of pre-surgical evaluation of drug resistant epilepsy. Before the FO placement, patients were evaluated with medical history, neurological and neuropsychological assessment, and magnetic resonance imaging (MRI) scans (T1 and T2). For surgical evaluation, scalp and FO electrodes were run simultaneous to the EEG recording using a digital video EEG system (Nihon Koden). Surface electrodes were placed on the scalp according to the international 10–20 system and placed sub

temporally according to the 10–10 system. Six-contact AdTech FO electrodes (Ad-Tech Medical, Oak Creek, Wisc.) with 5-mm intercontact spacing were inserted percutaneously under general anesthesia with the aid of intraoperative fluoroscopy, positioned so contact 1 was at the end of the ambient cistern and contact 6 was above the foramen ovale. CT scans were performed after electrode implantation for coregistration of electrode positions. In all patients, anticonvulsant medications were withdrawn in various amounts after FO placement to try to elicit seizures.

5.2.2. EEG and MRI data

EEG recording was done at 200Hz. An experienced electroencephalographer (AS) identified three 10-minute awake and three 10-minute asleep EEG segments totaling 1 hour of data, for each patient. These EEG segments were selected when the patient was resting with no rapid eye moment. Anti-epileptic medication was discontinued at least 24 hours before the sample time, and each sample was at least six hours away from any ictal activity. Ictal events were also isolated.

3D brain models for each patient were created from T1 MRI scans using Brainsuite(Shattuck and Leahy 2002). The FO electrode locations were identified from CT scans and superimposed on the 3D brain model using a locally developed method. The structural lesion boundaries were marked manually on sequential MR image slices and the 3D surface was rendered using Brainsuite.

5.2.3. Signal Analysis

Seizure onset regions and automatically detected interictal spikes on FO electrodes were verified by experienced epileptologists (JAL, AS). The FO spike data were processed through our previously established multistep dDTF algorithm (Biswajit Maharathi et al. 2018) that first requires accurate interictal spike detection(Daniel T Barkmeier et al. 2012) and time-locked spike segments, followed by evaluating the causal propagation of spikes. Briefly described, a rule-based algorithm first identifies epochs of interictal spikes to separate active time segments from periods of non-spiking background activity. Then, these specific time blocks are inspected for temporally consecutive spikes within 50 milliseconds. Such spikes on multiple channels were further isolated and grouped into time blocks. Each spike block started 750 milliseconds before the first spike peak and ended 750 milliseconds after the last spike peak.

To determine network propagation activity, each time block was extracted and further processed through discrete short-time direct directed transfer function (dDTF). dDTF is a previously established Granger causality-based model that predicts the flow of information between signal pairs in the presence of all other signals. First, spike blocks tested for stationarity using the Phillips–Perron test (~96.6% of spikes were stationary with $p<0.2$ when tested on individual spikes). Spike blocks were then processed using methods described previously(Biswajit Maharathi, Loeb, and Patton 2016; Biswajit Maharathi et al. 2018) where the entire signal was first filtered into specific frequency bands (20th order infinite impulse response filter), then fitted to a multivariate autoregressive model using modified covariance methods. Model order was determined by Akaike information criterion (AIC), corresponding to minimum AIC values (Model order: 13±12, minimum AIC value for each block: -0.0013±11, maximum model order: 50). The linear model was transformed to the frequency domain, and the resulting power spectra was used to identify partial coherence and full frequency-normalized direct transfer function (ffDTF). The dDTF is the linear product of the partial coherence and ffDTF and dDTF indicates the direction of information flow along with the strength of connection. Finally these values were statistically validated by exceeding the 95th percentile of 100 -fold phase-randomized surrogate data.(Biswajit Maharathi, Loeb, and Patton 2016; Biswajit Maharathi et al. 2018)

To investigate the propagation in narrow as well as broad frequency bands, we evaluated dDTF in isolated narrow bands such as delta (1-4Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), gamma (30–50 Hz) and a broad band at 1-35Hz.

5.2.4. Statistics

Pearson correlations were used for simple comparisons of propagation results. Multiple correlations used the correction $R^2 = c^T \mathbf{R}_{xx}^{-1} c$, where R is the multiple correlation coefficient, $c = (r_{x1y}, r_{x2y}, \ldots, r_{xNy})^T$ the correlations of r_{xny}, between independent variables Xn and dependent variable y, and $\mathbf{R_{xx}}$ is correlation matrix, defined as

$$\mathbf{R_{xx}} = \begin{pmatrix} r_{x1x1} & r_{x1x2} & \cdots & r_{x1xN} \\ r_{x2x1} & r_{x2x2} & \cdots & r_{x2xN} \\ & & \cdots & \\ r_{xNx1} & r_{xNx2} & \cdots & r_{xNxN} \end{pmatrix}$$

We used a threshold $\alpha=0.05$ for significance on all comparisons.

5.3. Results

5.3.1. Patient characteristics for interictal spike network analysis

Based on the successful application of dDTF to map interictal spike networks in neocortical epilepsy from subdural recording electrodes(Biswajit Maharathi et al. 2018), we asked whether interictal spike networks exist in patients being evaluated for temporal lobe epilepsy using bilateral FO recordings from 10 consecutive studies. Table 5.1 lists these patients with long-term, bilateral FO recordings of the mesial temporal surfaces as shown in Fig. 5.1A. All patients had simultaneous recordings from scalp electrodes. Four of these patients were lesional: two with unilateral hippocampal sclerosis, one with a teratoma tumor and one with focal dysplasia. Patients 5 and 10 were two separate recordings from the same patient with hippocampal asymmetry without sclerosis. The other 4 were either normal or showed diffuse atrophy on MRI. We captured seizures in all of the lesional patients and in one of the non-lesional patients. Medication withdrawal was performed to try to elicit seizures in all patients.

For each FO study, we selected six 10-minute EEG recordings with at least 100 interictal spikes (median spike count: 442±635) in each segment and evaluated the interictal spike networks. Spikes were detected using a validated spike detection algorithm(Daniel T Barkmeier et al. 2012). Fig 5.1A. Shows that while spikes often appear synchronous, they are not. By measuring the time delay between nearby spikes it is possible to map the spike propagation pattern for each spike. In Fig. 5.1B, we used the dDTF algorithm to map the spike propagation network of all time-locked spikes from each 10 min EEG recording. The result produces a probability map and directionality for each pair of electrodes for the 12 FO electrodes. The algorithm uses surrogate data based statistical validation to determine whether a spike will propagate between any pair of electrodes more than would be expected by chance. The end result produces a spike network map shown on the right-hand part of Fig. 5.1B that quantitatively summarizes all of the spike propagations and their direction as arrows within a given 10 min period. The thicker the line, the greater the number of spike propagations. To simplify the ‘wiring diagram’ to indicate the most common spike propagations in the network, we also show the top 10 percentile spike propagations.

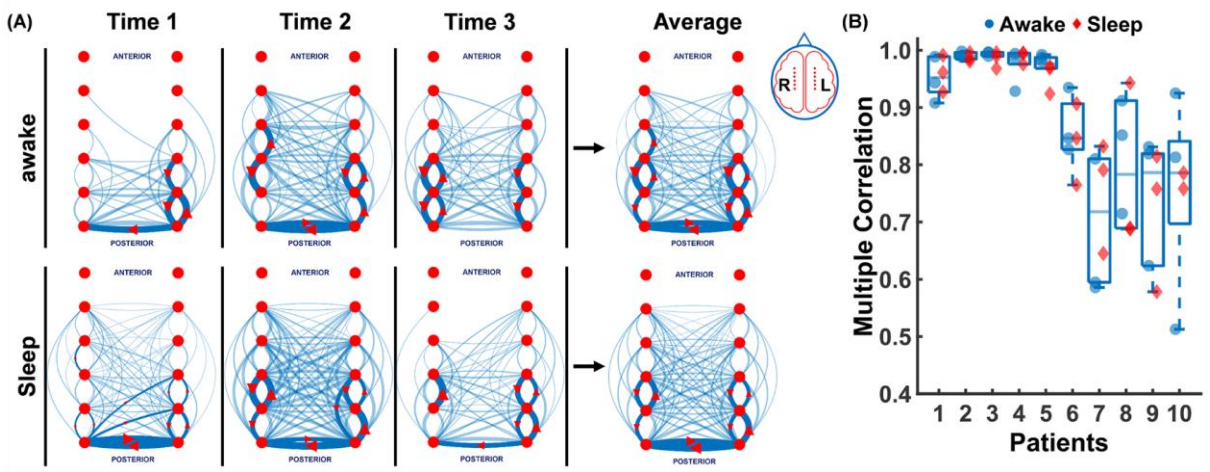


Figure 5.2. Interictal spike networks are highly reproducible and independent of sleep wake cycles. (A) The top 10% (solid blue lines with red arrow marks) and 90% remaining (faint blue lines) propagations are shown for patient 8 at three different awake and sleep 10 min intervals (Time1, Time2, Time3). Propagations here include all EEG activity between the broad band of 1-35 Hz. The average of the awake and sleep propagations are shown on the right panel which shows the high level of similarity for both wake and sleep spike propagations. (B) Multiple correlation coefficients across 3 sleep (red diamonds) and 3 awake (blue circles) 10 min EEG segments for each of 10 patients (0.93±0.13) is shown demonstrating the high reproducibility of the measured spike networks in both wake and sleep states.

5.3.2. Interictal spike networks are highly consistent within each patient and are not state dependent

Three of the six 10 min EEG segments were acquired during wakefulness and three in sleep. To measure the consistency of each patient's network and the relationship of the awake versus sleep state, we compared the interictal spike networks across both sleep and awake time segments. When analyzed in 1-35Hz broad frequency band as shown in Fig. 5.2A, we found that each patient had a highly consistent networks across all wake and sleep time periods (0.93±0.13) with no significant difference between awake and sleep ($p<0.05$) (Fig. 5.2B). Note that the interictal spike networks from patients 1-5, that were both mostly unilateral and lesional, were the most consistent.

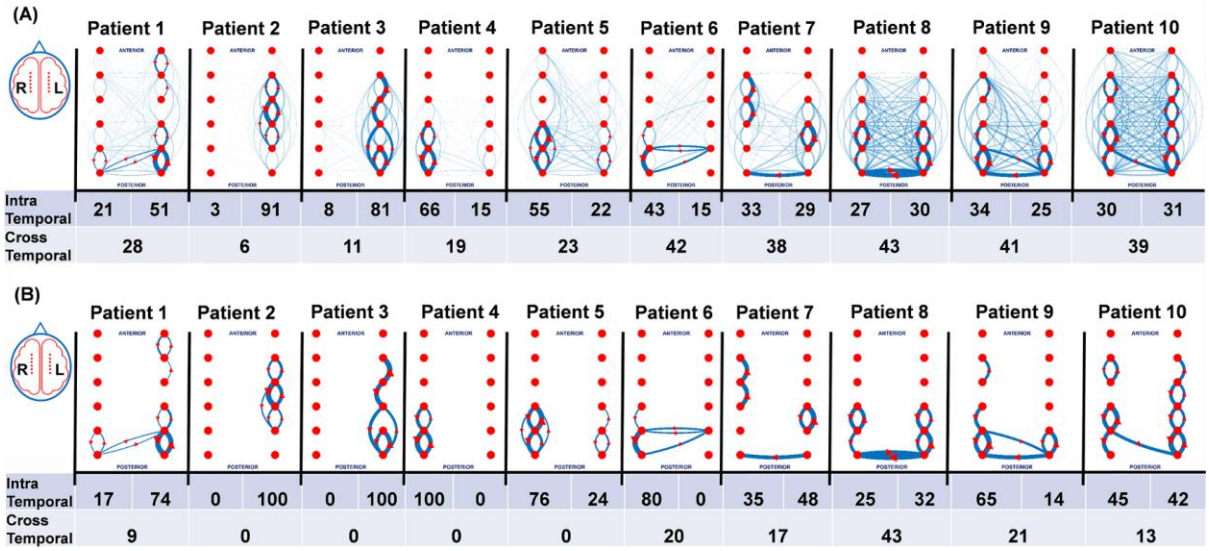


Figure 5.3. Each patient has a unique spike propagation network that can be unilateral or bilateral. (A) The total spike propagation network and the percentage that occur within (intra temporal) and between (cross temporal) temporal lobes are shown in the top panel. The solid blue lines with red arrows represent top 10 percentile of the propagation, and the faint blue lines represent bottom 90 percentile of the propagation. (B) Data for only the top 10th percentile propagations from panel A show simplified network schemata for each patient as well as the intra and cross propagation percentages. FO patient studies 1-5 were mostly unilateral, whereas 6-10 had a mix of intra and cross temporal propagations that may be related for some to the presence of ipsilateral lesions.

5.3.3. Interictal spike networks are patient-specific, multidirectional, and cross over to the contralateral temporal lobe

Fig. 5.3A shows the interictal spike networks for each patient together with their top 10th percentile network (Fig. 5.3B). No two patients had the same networks. Within each network, spikes propagated both within and between temporal lobes. Spikes sometimes had a clear directionality of spread: for example from anterior to posterior or posterior to anterior. For many brain regions spike networks were bidirectional and reverberated between two or more sites. In addition to spike propagations within a given temporal lobe, spikes also frequently propagated between temporal lobes. For each patient, the percentage of spike propagations within each temporal lobe (intra temporal) and between the two temporal lobes (cross temporal) are shown. Intra temporal propagations (67±13%) were significantly higher than cross temporal propagations (33±13%) in 9 out of 10 patients ($p < 0.05$) suggesting most of the propagations remain within

the same temporal lobe. The patient with studies 5 and 10 is the same patient that was recorded twice (the earlier recording is 10, the recording done the following year is 5). Study 5 showed unilateral spike networks without cross temporal propagations, study 10 instead had bilateral spike networks with significant cross temporal propagations. It is possible that either medication differences (clobazam stopped the day prior to the recording) or the presence of a vagus nerve stimulation device placed prior to study 5, but not present for study 10, prevented these cross temporal propagations and kept the spike network unilateral. In patient 7, although the intra temporal propagations were higher than the cross-temporal propagations, it was not significant ($p < 0.1$). Interestingly, most cross temporal lobe spikes utilized posterior rather than anterior anatomical connections. Of note, we did not see any significant effect of sleep or awake states on cross temporal propagations in any patient (data not shown).

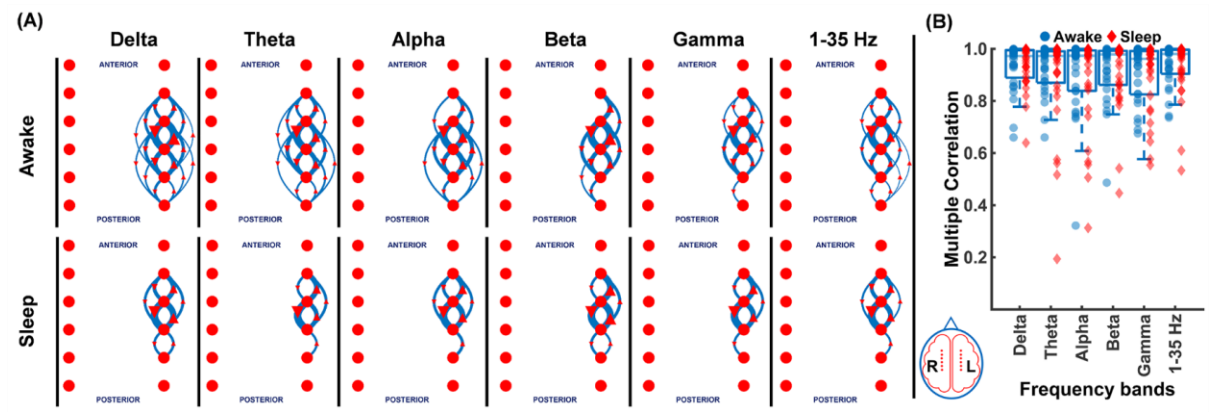


Figure 5.4. Interictal spike networks are highly reproducible across different frequency bands. (A) The top 10 percentile spike propagation patterns at delta, theta, alpha, beta, gamma frequency bands, and 1-35 Hz broadband shown for patient 2 are remarkably similar. (B) Multiple correlation coefficients (0.97±0.006) for each frequency band across all patients during sleep (red diamonds) and awake (blue circles) are quite similar.

5.3.4. Interictal spike networks are strongly influenced by brain lesions

In lesional patients, propagations were primarily ipsilateral to the lesion (patients 1-4). The patients without brain lesions (patients 6, 7, 8, and 10), had comparable propagations within each temporal lobe and had the most cross temporal propagations. Patient 9 had an MRI documented reduction in the volume of the anterior hippocampus with no sclerosis. While his spike propagations were bilateral and cross

temporal, there were very few propagating spikes over the region with reduced hippocampal volume and most of his spike network involved the contralateral (right) side.

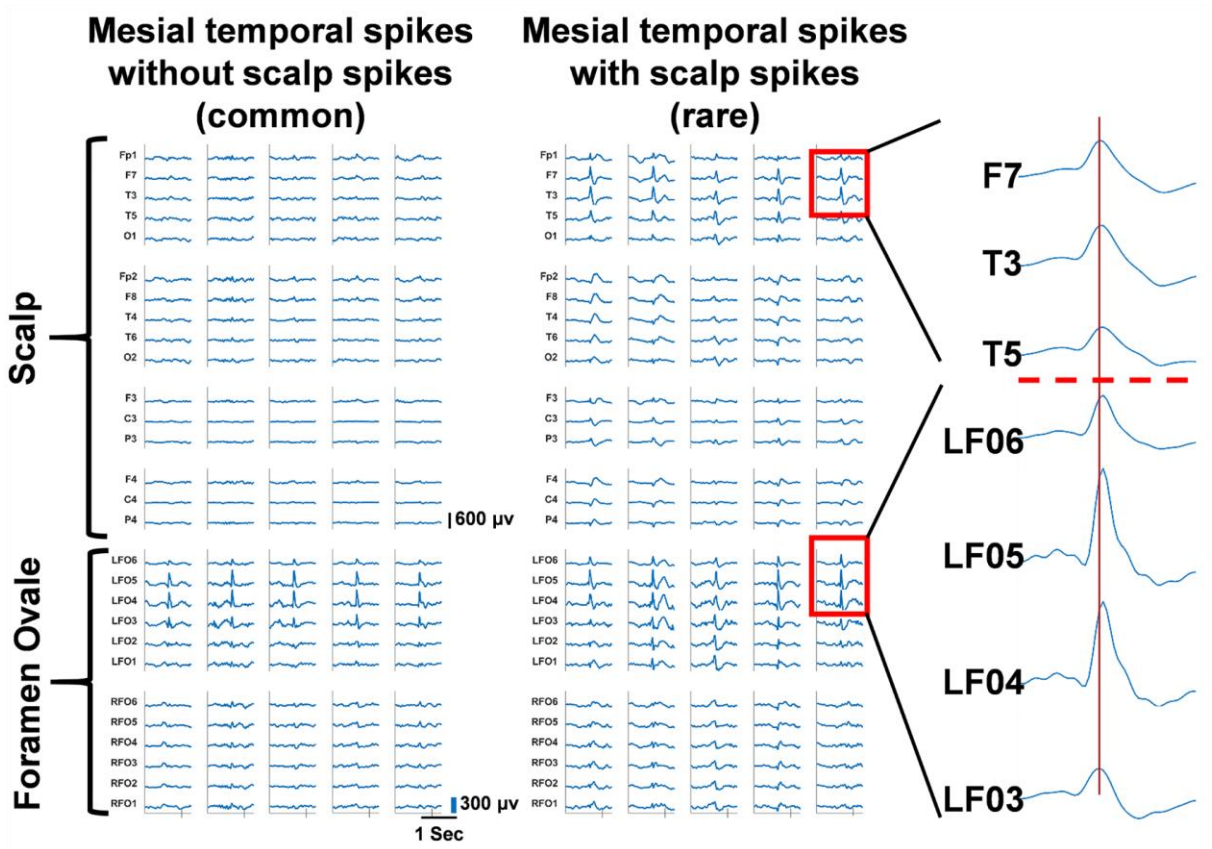


Figure 5.5. Medial temporal spikes rarely appear on scalp electrodes and are have no clear propagation pattern. Medial temporal spikes recorded from FO electrodes (L3 – L6) show synchronous interictal spikes with the scalp leads only 4% of the time (left) at (F7, T3, T5) (right) for patient 2. A zoomed in visual of the spike events on FO electrodes and scalp electrodes show highly synchronous FO and scalp EEG spikes with no consistent time delays between FO and the scalp events, suggesting no clear pattern of propagation between these two recording sites.

5.3.5. Interictal spike networks are consistent across frequency bands

Given the growing interest in the predictive value of different frequency bands, we analyzed the interictal spike networks across delta, theta, alpha, beta, gamma, and broad bands (1-35 Hz). This is shown for patient 2 in Fig. 5.4A and for all patients in Fig. 5.4B. We did not find any significant differences in spike propagations on EEG data filtered for each of these frequency bands or as a function of specific awake and sleep cycles. While both low and high frequency bands had highly reproducible networks (0.97±0.006)

within each patient, we failed to find any frequency-dependent differences. Although broad band and delta band appeared to have slightly higher connection density, no significant difference between other frequency bands were observed. We also noticed that the patient subgroup who had highly conserved networks in broad bands, did show higher network similarity across different frequency bands (median: 0.99) compared to the subgroup that had lower network similarity in broad band (median: 0.90). We did not specifically examine high frequency oscillations due to the limitations of our recordings, recorded at 200 Hz.

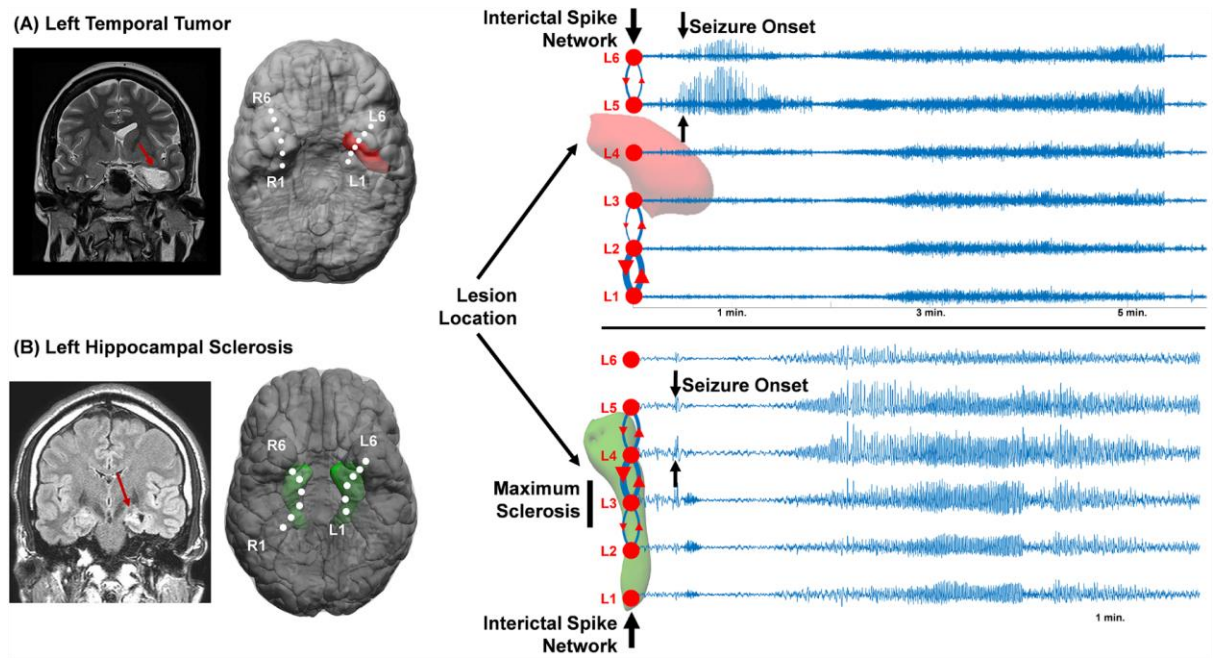


Figure 5.6. Relationships between interictal spike networks, structural lesions, and seizure onset zones. (A) Patient 1 had a teratoma tumor in the mesial temporal lobe that was coregistered to the FO electrodes. The top 10 percentile interictal spike network is shown in relation to the lesion and seizure onset zones. (B) Patient 2 had left hippocampal sclerosis with a smaller hippocampus and a bright MRI FLAIR signal. The interictal spike network and seizure onset zones were both present at the L4 and L5 electrodes which were on the edge of the sclerotic region.

5.3.6. Mesial temporal spikes cannot be detected on surface EEG and do not clearly propagate to the cortical surface

Previous studies using both intracranial and surface electrodes have shown the limitations of surface leads to detect EEG activities in deeper structures, such as the mesial temporal lobe(Lam et al. 2017; Velasco et al. 2006) . An unanswered question is whether spikes that are detected by surface EEG

in deep structures are detecting spikes generated from these deep structures via volume conduction or whether they are propagating to the cortical surface. We measured ~8000 time-locked spike blocks on FO electrodes and determined the percentage that coincided with scalp EEG spikes. On average, only 4% of mesial temporal spikes coincided with scalp EEG spikes. This finding is in line with previously published results(Lam et al. 2017). However, when we used the dDTF function to determine the directionality of propagation, we did not find clear evidence of mesial temporal spikes propagating to scalp or vice versa. These findings confirm that surface EEG spikes are not generated from deeper temporal structures by volume conduction, but do not establish a clear propagation pattern in either direction for those spikes that appear synchronous between mesial and lateral temporal lobe structures.

5.3.7. Spike networks relate to seizure onset and lesion location

While the present series is limited in the number and similarity of patients in this retrospective analysis, we explored the relationships between interictal spike networks, seizures, and lesion locations in those with lesions in the hope that this type of analysis could in the future aid in surgical and non-surgical planning. Only 5 of 10 patients had seizures recorded and of these only two had clearly defined lesions and focal seizures (patients 1 and 2, Table 5.1). The relationship between lesion, seizure onset, and spike networks are summarized in Fig. 5.6 for these two patients.

Patient 1 had a teratoma tumor adjacent to the left hippocampus extending to the left temporal lobe. The L4 electrode was closest to the tumor, however, had very few spikes. The interictal spike network predominantly split into two regions: L1-L3, posterior to the tumor, and L5-L6, anterior to the tumor (Fig. 5.6A). Maximal spike reverberation occurred between L1 and L2. Three recorded seizures were generated anterior to the tumor at L5-L6 with subsequent spread to other electrodes. While the most active subnetwork involved the posterior electrodes (L1-L3), it was the anterior L5-L6 spike network that perfectly aligned with the seizure onset zone.

Patient 2 had left hippocampal sclerosis with maximal MRI FLAIR signal and volume loss seen at L3 (Fig. 5.6B). The spike network for this patient was broad from L2-L5 with maximum reverberations at L3-L4, just anterior of the region of maximum sclerosis. Three out of 4 seizures recorded had onset starting

further anterior to the sclerosis that started with heralding spikes at L4-L5 followed by spread to L2-L3 posterior to the sclerosis and then more uniform ipsilateral involvement throughout the temporal lobe.

While the present series is limited, the use of dDTF for these 2 lesional patients reveal that both spikes and seizure networks were adjacent to rather directly coming from the lesions. These examples also demonstrate that while a portion of the spike network overlaps perfectly with seizure onset, other portions of the network, often with the highest level of spiking occur at independent locations from the seizure network, suggesting that not all spike networks may be related to the production of seizures.

5.4. Discussion

Interictal spikes have been suggested to be a significant biomarker of epilepsy and are hypothesized to arise from the cumulative synchronous firing of millions of underlying neuronal cells. The concept of the epileptogenic focus has been recently revised to a broader definition of an “epileptogenic network” that includes different brain regions, amongst which hippocampus is a key player. Understanding networks is extremely important for targeting therapies such as focal ablation and neuromodulation. Previous studies have shown that interictal spike networks are ‘hard-wired’ in their propagation patterns in the neocortex, are highly consistent within a given patient, but highly unique for each patient (Biswajit Maharathi et al. 2018). Here we demonstrate a similar hard wiring of interictal spike networks in patients being evaluated for temporal lobe epilepsy. These networks are independent of the sleep-awake state and indistinguishable at different frequency bands, similar to what has been seen in the neocortex (Biswajit Maharathi et al. 2018). This suggests that spike propagations have multiple frequencies in their signals that propagate together.

We were able to map these interictal spike networks in the temporal lobes using the causality based dDTF algorithm on intracranial recordings obtained with bilateral foramen ovale leads in 10 consecutive FO studies of epileptic patients. Patients with brain lesions had the most consistent spike networks and tended to be unilateral compared to non-lesional patients. On the other hand, non-lesional patients had more bilateral propagations involving both temporal lobes along with cross-temporal propagations. Spikes propagated in both anterior and posterior directions along the mesial temporal surface and most cases, reverberated in both directions. This was particularly prominent in lesional patients where spike reverberations occurred near the lesion and did not cross to the other temporal lobe. Surprisingly, most

cross-temporal lobe propagations occurred through the posterior electrode positions, suggesting usage of the hippocampal commissure within the fornix rather than the anterior commissure as the anatomical pathway for spike propagation.

It is generally well-accepted that patients with temporal lobe lesions seen on MRI have a better surgical outcome than those without lesional forms of epilepsy (Clusmann et al. 2004). Lesional patients in our series had more restricted and unilateral interictal spike networks compared to non-lesional patients, who generally had bitemporal networks with more frequent spike crossing between the two temporal lobes. Non-lesional patients from our series either had no clear seizures or seizure onset zones outside of mesial temporal lobe structures. On the other hand, lesional patients had seizure onset zones that overlapped portions of the interictal spike network but were not at regions of the network with the highest levels of interictal spiking. The remarkable reproducibility of spike networks near or around lesions suggests that measuring these networks prior to lesion resections could improve patient outcome by reducing seizures or preventing the development and growth of epileptic networks that can occur over time if networks are left in place.

While our series is limited, both the spike networks and seizure onset zones mostly involved lesion borders. The lesions themselves, including tumors and hippocampal sclerosis, had reduced spike networks and were not the sites of seizure onset. Spike propagations commonly reverberated at the perilesional boundaries. Other studies highlight this observation. One study showed that peritumoral spikes are most frequent and can be sharper than other interictal spikes (Mittal et al. 2016). Similarly, studies in tuberous sclerosis infants suggest that epileptic spikes are often seen long before they have their first seizure and the spikes often localize with seizure onset zones that are peri-tuberal (Wu et al. 2016). Perhaps this is not surprising given that many tumors, including the teratoma here, are not themselves capable of generating epileptic activity. In the case of hippocampal sclerosis, sub-regions of the hippocampus with the most gliosis and neuronal cell loss are likely not be capable of generating epileptic activities as easily as adjacent, more intact regions of the hippocampus.

Consistent with other studies, we found that only 4% of mesial temporal spikes seen with the FO electrodes were time-locked with spikes on scalp electrodes. Patients with lesional epilepsy had high

amplitude scalp spikes that were closely time-locked with spikes seen with the FO electrodes, and were always lateralized to the side of the lesion. Non-lesional patients who had less well-formed spike networks on the FO electrodes, didn't have synchronous scalp spikes. However, unlike spikes within or between the mesial temporal lobe structures, coincident spikes in the lateral temporal cortex (seen by FO and surface electrodes at the same time) had no clear directionality of spread. These results strongly suggest that temporal lobe spikes detected with scalp EEG are not being detected from mesial temporal structures by volume conduction, but instead are being generated by the neocortex closest to the surface EEG electrodes. Previous studies looking at neocortical spikes detected by subdural grids and surface EEG concluded that cortical sources of scalp EEG spikes require the synchronous activation of at a minimum of 6-10 cm^2 of neocortex, with 20−30 cm^2 needed to produce prominent scalp EEG spikes (Tao et al. 2005). The fact that there was no clear directionality of spread between FO and surface-detected spikes, suggests that the onset of the spike may be generated somewhere between medial and lateral structures. It is also possible that lesional patients recruit a larger neuronal network than non-lesional patients thus generating larger interictal spike fields that more readily propagate to the cortical surface.

It has been postulated that bilateral (bitemporal) discharges are the consequence of the progressive nature of epileptogenesis (Morrell 1989). Based on this, it was thought that the longer the duration of epilepsy, the more likely it will spread to the contralateral side. Within our patient cohort, we did not see a clear correlation between age of onset and duration of epilepsy, but instead identified the lack of temporal lobe lesions as the strongest indicator of bilaterality. Interestingly, the same patient recorded on two separate occasions (patient 5 and 10) was initially bilateral (10), but became unilateral (5) while taking the medication clobazam and having vagus nerve stimulation. This observation demonstrates the potential to explore the specific effects of medications and other treatments on interictal spike networks as a potential therapeutic approach. It also supports the effect of neuromodulation on spike networks.

Taken together, while the current study has limitations in cohort size, electrode coverage, and diversity of patients, it provides the first clear evidence for highly reproducible interictal spike networks that are closely linked to both lesions and seizure onset brain regions. Our results show that the most consistent of these spike networks and seizures come from the perilesional tissues. Non-lesional patients have spike

networks that are more diffuse, and more often bilateral. Interictal spike networks in patients with temporal lobe seizures had a portion of their spike network that precisely overlapped with their seizure onset zone, but also had other portions of their spike network, often with higher levels of spiking, that were spatially distinct from seizure onset. Further studies will be needed to delineate both spatial and temporal relationships between interictal spike networks and seizures and to see if interictal spike networks could be used to predict seizure onset zone location or when a seizure is going to occur. Measuring these networks in advance of surgical resections could determine which spiking regions need to be removed for better postsurgical outcome. Findings from these studies will advance our ability to perform less invasive treatments of epilepsy. Given the expanding use of closed loop and direct stimulation devices for the treatment of refractory epilepsy, a precise spatial and temporal understanding of interictal spike and seizure networks could vastly improve the utility of these and other devices and approaches.

VI. INTERICTAL SPIKE PROPAGATION HUBS PREDICT SEIZURE ONSET ZONES IN NEOCORTICAL EPILEPSY

6.1. Introduction

Refractory epilepsy often results in intractable seizures and needs surgical intervention. In such cases, pre-surgical evaluation needs to delineate the epileptogenic and adjacent eloquent areas accurately. While recurrent seizures recorded on EEG are the most reliable way to identify the seizure onset regions, their infrequent nature limits our ability to rely on them entirely. The alternative reliable EEG biomarker to seizure is the interictal spike. These interictal spikes are brief, but sharp electrical events, frequently occurring between consecutive seizures and are often located in the seizure onset regions. Along with EEG measurements, brain lesions or structural abnormalities observed on MRI also help pinpoint the epileptogenic tissue locations (Wyllie et al. 2007). However, there is no clear consensus in the field delineating the relationship between epileptic seizures, interictal spikes, and brain lesions.

Existing literature on brain lesions such as tuberous sclerosis, cortical dysplasia, and other lesions related to epilepsy suggest that complete removal of structurally-marked lesions significantly improves the post-surgical outcome (Oluigbo et al. 2015; Awad et al. 1991; C. Lee, Jeong, and Chung 2019). The study conducted on tumor-related epilepsy also suggests that the extent of resection is not a measure of postoperative seizure outcome, and complete removal of the tumor is a better approach (C. Lee, Jeong, and Chung 2019). Other studies on the temporal lobe epilepsy suggest only 70% of surgical interventions have good outcomes in lesion related epilepsy, and additional tissue removal around the lesion may not further improve the seizure outcome (Clusmann et al. 2004). Although lesion removal helps improve outcomes, tumor resection in tumor-related epilepsy does not always provide an optimal outcome (Englot et al. 2012, 2011). Other studies suggest taking additional tissue around the tumor margin for better outcomes (Mittal et al. 2016). Hence structural guidelines are not only unclear, and not all patients have structural markers visible on MRI.

Alternatively, physicians and researchers have widely pursued interictal spikes to localize epileptic foci because of their frequent occurrence in refractory epilepsy. The source analysis of these interictal

spike peaks suggests that they occur near lesion regions identified on MRI (G. Wang et al. 2011). The interictal spike source could also accurately indicate epileptic foci (Brodbeck et al. 2009). In tumor-related epilepsy, interictal spikes occurring close to tumors were lower in amplitude and less sharp while peritumoral interictal spikes had higher occurrences and sharper slope (Mittal et al. 2016). Also, interictal spikes in seizure onset regions (SOZ) were frequent and had a higher power, removal of which resulted in excellent seizure outcome (Mittal et al. 2016). It is clear that intervention might be better guided.

One suggestion is to focus instead on the propagation of interictal spikes rather than the events themselves, as epilepsy has been hypothesized as a network disease that alters connectivity. In such a case, it is essential to understand the dynamics of this network evaluated from the epileptic events such as spike and seizures and study the relationship of this network with seizure onset and lesion location. It is essential to explore the dynamics of interictal spikes and seizures in lesional patients versus non-lesional cases to identify common and unique features for each. Previous studies suggest that Interictal spikes have a patient-specific reproducible network (Biswajit Maharathi et al. 2018). These networks also can predict seizure onset regions in most cases (B. Maharathi, Loeb, and Patton 2019). Chapter 5 found that the interictal spike network reverberates in peri-lesional tissue in temporal lobe epilepsy. However, the ways a network might transmit information amongst its constituent parts is complex and needs tools that can appropriately analyze the many ways signals might propagate. We assert that the network analysis tools from graph theory can help diagnose epileptic brain regions and identify targets for intervention.

In the present Chapter, we evaluated interictal spike propagation networks and different centrality measures for the network in 23 neocortical epilepsy patients admitted for epilepsy surgery. We related several graph centrality metrics to seizure onset, lesion location, and high spiking brain regions. This extends our previous work (B. Maharathi, Loeb, and Patton 2019) to cover wider brain regions in a more extensive series of lesional and non-lesional patients with a stronger focus on seizure onset.

6.2. Methods

6.2.1. Patient selection and data collection

Twenty-three intractable epilepsy patients with recurrent seizures were selected under a protocol approved by Institutional review board at University of Illinois at Chicago. All the patients went through two

stage epilepsy surgery, where large number of subdural electrodes were implanted on their neocortex for long term monitoring.

Table6.1. Patient Information

Patient ID	Age	Sex	Pathology	Spike Count/ 10 minute
EP122	**15**	female	Polymicrogyria	311
EP124	**10**	male	Polymicrogyria	4325
EP129	**29**	male	Focal cortical dysplasia	3624
EP132	**10**	female	gliosis	61695
EP138	4	female	polymicrogyria	4707
EP142	**8**	male	TSC	4269
EP143	**11**	female	**Heterotopia**	4716
EP156	2	male	gliosis	28640
EP158	1	male	gliosis	19198
EP160	1	female	gliosis	12016
EP162	1	female	Polymicrogyria	6111
EP164	3	female	gliosis	18053
EP165	3	female	gliosis	16572
EP169	**8**	male	gliosis	6479
EP173	2	male	gliosis	19941
EP183	**22**	Female	Hemiparesis	10397
EP187	5	Male	TSC	7543
EP188	**16**	Male	Large cyst	6033
EP195	7	male	gliosis	11177
EP196	2	male	gliosis	3119
EP199	2	male	TSC	12694
EP201	**15**	female	gliosis	1384
EP202	3	male	TSC	11597

Electrocorticography (ECoG) data was recorded at 1000 Hz using 192 channel Nihon Kohden Digital System (Nihon Kohden America Inc, Foothill Ranch, CA, USA) with subdural electrodes (4 mm in diameter and spaced 10 mm apart, PMT platinum electrodes, PMT Corporation, Chanhassen, MN, USA). Three patients were recorded at 200Hz sampling rate. An experienced EEG reader extracted three 10-minute ECoG time segments for each patient from three different days when adequate interictal spikes were observed and patient was resting with eyes closed. It was made sure that there were no seizures

within 6 hours of the sample dataset. T1/T2 MRI scans before surgery were collected for each patients for identification of the any structural lesion or abnormality. Further intraoperative images and CT/ X-ray scans were collected post electrode implantation, for accurate localization of the electrode positions.

6.2.2. Image processing

3D brain models were created for each patient from T1 MRI using BrainSuite 19a. Implanted electrode locations were co-registered on the 3D surface using CT scan and visually verifying the electrode positions from x-ray and intraoperative images. A mask was created for each lesion or abnormality on T1 MRI manually using Brainsuite and surface was rendered so that we can visualize 3D model of the brain along with lesions and implanted electrode locations.

6.2.3. Signal Analysis

We followed a previously established protocol (Biswajit Maharathi et al. 2018) to evaluate the interictal spike propagation in neocortex. Briefly, Interictal spikes were automatically marked on the EEG files using a previously established algorithm (Daniel T Barkmeier et al. 2012) and verified by experienced epileptologists (JAL). The interictal spikes were further analyzed by an algorithm to find the series of consecutive spikes that align with their peak to peak distance within 50 milliseconds. A series of such time-locked spikes on multiple channels are called a spike block. Once the spike blocks are detected in each files, we isolated spike data of length 500 milliseconds before the peak of first temporally occurring spike and 500 millisecond after the last spike peak in the same spike block.

Further, we used Granger causality based direct directed transfer function (dDTF) to evaluate the spike propagation within each spike block. First, isolated spike block are extracted and filtered to 1-35 Hz frequency band using a 50th order zero phase band pass infinite impulse response filter. Next, this filtered signal was fit to a multivariate auto regressive model with a model order predetermined by Akaike information criterion (AIC). The optimum model order selected corresponded to the minimum AIC value. The maximum allowed model order was set to 50. Further the modeled dataset was transformed to frequency domain and dDTF was calculated. The dDTF estimates the direct propagation between a pair of channels while accounting the effect of all other channels. The estimated dDTF was validated by exceeding

95th percentile of dDTF response to 100 phase randomized surrogate dataset generated from the same spike block. The similar procedure was applied to all the discrete spike blocks present in the dataset.

The evaluated propagations were further used to construct directional graphs and relationship of spike propagation with seizure onset and lesion location. Appropriate statistical measure were used for each type of analysis and details are provided along with the results as appropriate.

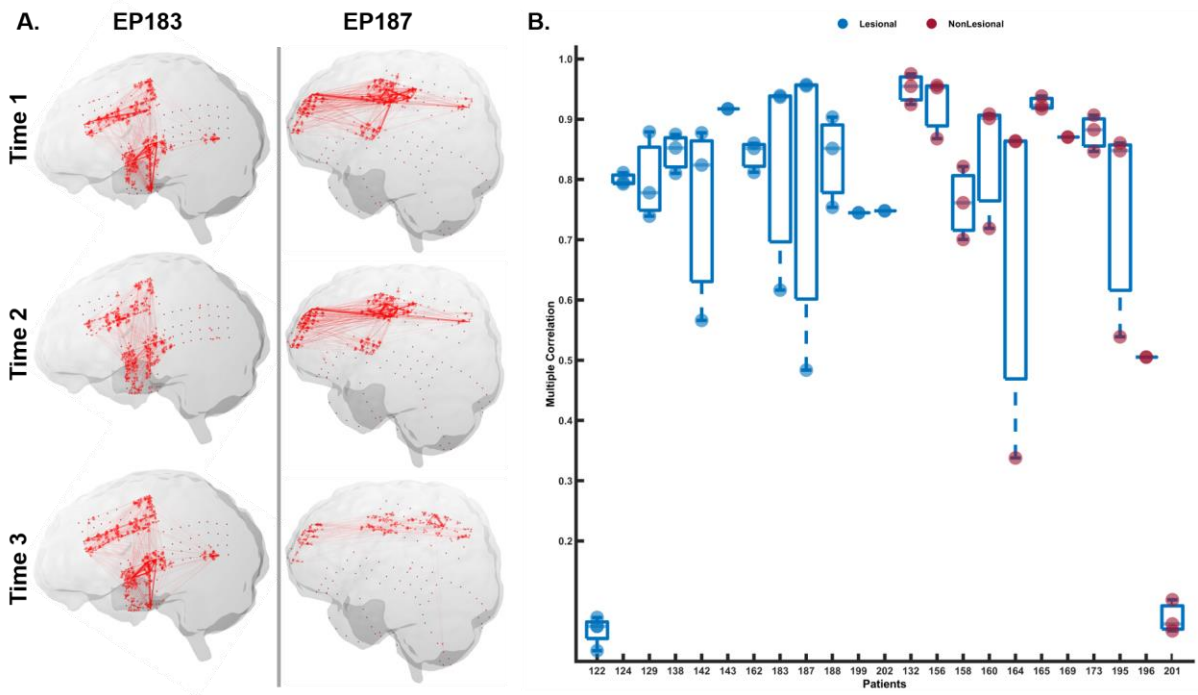


Figure 6.1. Interictal spike network is reproducible across time but patient specific. (A) Reproducible interictal propagation pattern in two different patients EP183 and EP187. For each patient, the spike propagation at three different time points is very similar. For easy understanding only top 10 percentile of the network is shown. Each line thickness shows how often the pair of electrodes propagated in 10 minutes, and the arrow mark shows the direction of propagation. (B) The interictal spike propagation similarity among three 10-minute time segments evaluated using multiple correlation coefficient. The box plots with blue data points are for the patients who had lesions identified on MRI/ pathology test. The box plots with red data points are for the patient without any identifiable lesion. Most of them had gliosis.

6.3. Results

We obtained recordings from electrodes placed on the neocortex in 23 epilepsy patients who underwent epilepsy surgery. Table 6.1 lists these patients. The patient population (median age: 5±7.4, range: 1-29, 10 female, 13 male) was divided into two groups based on the presence or absence of lesions

on their MRI. The nine non-lesional patients had mild gliosis, whereas the 14 lesional patients had diverse lesions on their MRI or their pathology reports, including four patients with polymicrogyria, four with tuberous sclerosis, one with focal cortical dysplasia, one with heterotopia, one with an arachnoid cyst, one with stroke, one with a large cyst and one with gliosis. Amongst the lesional cases, the lesion location could be observed on the MRI in only seven of the patients.

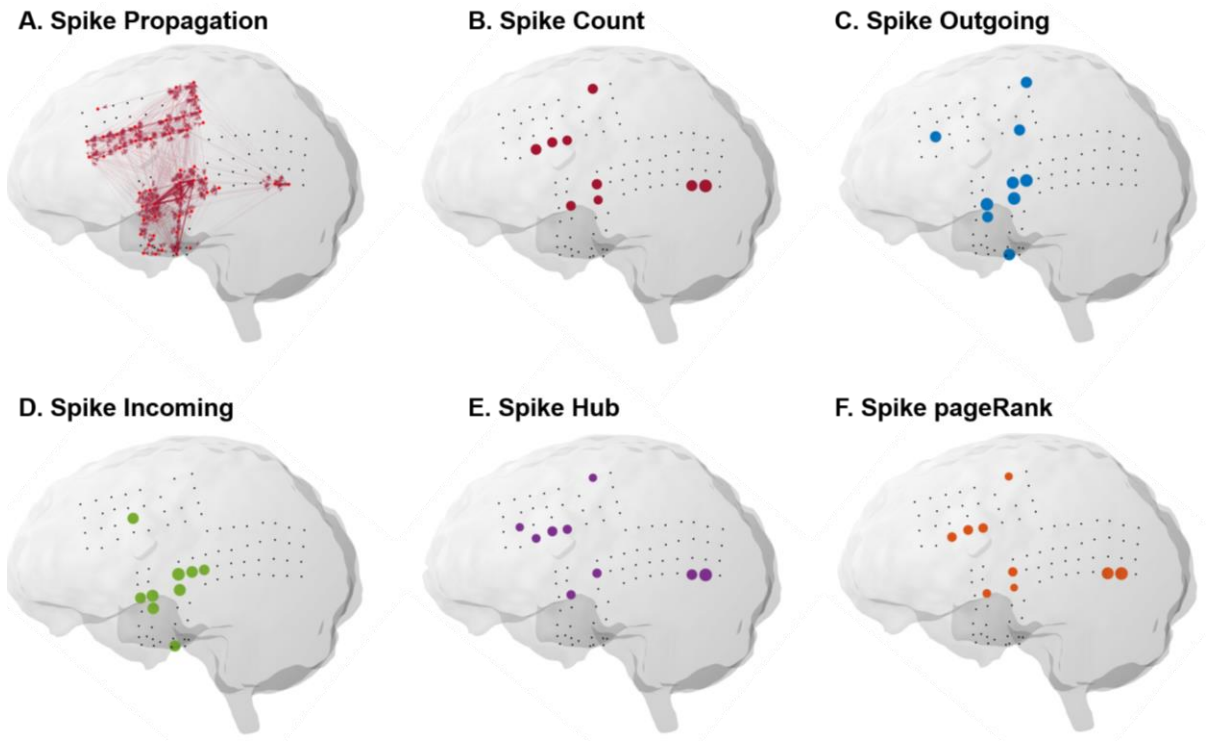


Figure 6.2. Electrodes with high spike counts are best associated with PageRank and Hub characteristics. (A) Shows the top 10 percentile propagations after aggregating all the propagations in 30 minutes for patient EP183. (B) Shows high spiking electrodes after thresholding 90% spikes. (C), (D), (E), and (F) shows the top 10% electrodes after thresholding the Outgoing, Incoming, Hub and PageRank centrality measures, respectively.

For each patient, we selected three 10-minute ECoG segments. Each patient had 96±8 electrodes placed on the neocortex with at least 1000 interictal spikes in 10 minutes (median: 9371± 13414) except for EP122 where fewer than 1000 spikes were marked. We used the dDTF algorithm to map the interictal spike propagation for each patient using isolated time-locked spike epochs. Amongst all the spike in all the patients, 85±11% spikes were found to be propagating. Using the evaluated spike network, we investigated the spike network's reproducibility at different time points in each patient, the relationship between high

spiking electrodes and spike propagation centrality measures, the relationship between interictal spike network with lesion location and seizure onset zones in each patient.

We found that interictal spike propagation was consistent across time and agnostic of lesion and seizure locations (Fig. 6.1). First, we evaluated the count of propagations for each pair of the electrode in each patient's 10-minute file. We removed any electrodes from analysis with one or zero propagations in the 10-minute data segment. Further, we took the propagation counts for each electrode pair across all three segments and calculated the multiple correlation coefficient. The interictal spike network was highly reproducible in each patient (median correlation 0.8±0.15) except for two patients EP122 and EP201. The median correlation in these two patients was 0.002, suggesting no reproducibility of the spike network in these two patients for the selected time segments. We further evaluated the number of propagation going out from each electrode and compared that across all three ECoG segments and found similar observation (median correlation: 0.85±0.14) except those two patients in which case median multiple correlation coefficient was 0.06.

We checked overall spike propagation similarity in patients with lesions identified by MRI or pathology and compared with patients with gliosis or no identifiable lesion on MRI or pathology. Overall, when evaluated with student's t-test with equal mean but unequal variance, we did not find any significant difference between the two patient groups.

We further separated the propagations to only seizure onset zone electrodes (SOZ) and compared them for reproducibly of spike propagation against non-seizure onset electrodes (non-SOZ). We did not see any significant difference in spike propagation reproducibility between SOZ electrodes and non- SOZ electrodes (Kruskal-Wallis one-way ANOVA, combined with all patients p=0.185). We further divided the patients into lesional and non-lesional groups, as explained above, and performed a similar test on SOZ vs. non-SOZ. There was no significant difference between SOZ electrodes and non-SOZ electrodes in spike propagation (p=0.7) in patients with brain lesions; however, in the non-lesional patient group, the difference between SOZ vs. non-SOZ electrode group was significant (p=0.02).

We also found that seizure onset s was better associated with spike propagation hubs than spike count. We conducted comparisons between spike propagation centrality measures and seizure onset

regions to find the best centrality measures that accurately predict seizure onset zones (Biswajit Maharathi et al. 2018). For this, we considered several parameters starting with spike count, outgoing, incoming, hub, authority, PageRank, and betweenness centrality. First, we implemented a graduated threshold method from 5-95% for each measure and calculated the receiver operator curve (ROC). We further computed the area under the curve and the closest point on the curve to the (0, 1) point for each centrality measure and each patient from the ROC curve. For any of the parameters under consideration, the median threshold ranged between 42-49 percentiles across all patients. For further computations, we used the 50-percentile threshold. We found that the performance of the graph centrality measures predicting seizure onset zones is very patient-specific. Eleven out of 21 patients had significant seizure onset prediction from any of the graph centrality measures and simple spike count ($p<0.005$, Fisher exact test). These 11 patients also had a higher area under the ROC curve (0.74±0.15) than the rest of the ten patients (0.46±0.14). Overall, hub centrality was the best seizure onset predictor (14/ 21 patients, $p<0.005$, Fisher exact test, median Critical success index: 47±21), and betweenness centrality was the worst predictor of seizure onset (9/21 patients, median Critical success index: 43±21). We excluded Patient EP122 and EP201 from the analysis because of their low reproducibility of spike network propagation.

Spike propagation often reverberated in perilesional regions. While the present series of patients have diverse pathologies and MRI lesions, we explored the relationship between lesion location observed in MRI and spike network. In the current patient cohort, only 7 of 23 patients, apparent anatomical lesions/ abnormality, were seen on T1/T2 MRI. Using available MRI scans, we reconstructed the 3D model of the brain and modeled the lesion location. Further, the electrode grids were co-localized on the 3D brain surface using available CT/ X-ray scans and intraoperative images. We investigated the high spiking locations and spike propagation centrality measure and compared them with seizure onset and lesion location.

Patient EP129 had focal cortical dysplasia on the right frontal lobe, and the right temporal lobe was abnormally small compared to the contralateral side (Fig. 6.3A). We observed most of the spiking on the cortical dysplasia and spiking adjacent to the temporal lobe. These areas also had frequent spike propagations with a reverberating pattern. The seizure onset was also on the same locations did not completely overlap with any of the interictal propagation centrality measures.

Patient 188 had a large cyst on the right side, mostly on the occipital-parietal lobe (Fig. 6.3B). The interictal spike propagation was primarily on the temporal lobe, anterior to the cyst, and the lateral occipital electrode strip. PageRank and hub centrality measure for the interictal spike propagation aligned with the seizure onset electrodes on the occipital lobe, but there was limited overlap on the anterior areas of the lesion.

In the case of patient EP187 (TSC) and EP183 (Stroke), the spike propagation was on the peri-lesional regions, and spike propagation centrality measures had limited overlap with seizure onset regions (Fig. 6.3C & D). Other lesional cases also had a similar observation.

While the present series of patients is limited, and the lesions have diverse pathologies, the spike propagation reveals that the spikes and seizures come from adjacent lesion regions. However, a direct relationship between spike network centrality measures and seizures is limited, suggesting the existence of an independent lesion driven spike network. The spiking network observed far from the lesion location might also be independent.

High spiking electrodes have high relative importance (PageRank). To understand the relative importance of high spiking electrodes in terms of graph measures, we compared it with different node centrality measures of the interictal spike propagation. We calculated indegree, outdegree, betweenness, hub, authority, and PageRank centrality measures for each spike block. Further, for each node, we calculated the net centrality value by aggregating respective centrality scores over 30 minutes of ECoG (Fig. 6.2). Once we got the centrality measure for each node in each patient, we further thresholded to 90 percentile and only took the top 10% of the electrodes for each centrality measure and compared it with the top 10 percentile spiking electrodes, where the spike count was also aggregated over 30 minutes. High spiking electrodes had a significantly higher page rank score (median Critical success index for PageRank: 78±21, $p<0.005$, fisher exact test, $h=1$ for all patients). These high spiking nodes also had a better chance of becoming network hubs (median Critical success index for hub: 67±19, $p<0.005$, fisher exact test, $h=1$ for all patients) and often higher closeness centrality. Betweenness centrality did not have a good association with high spiking electrodes (median Critical success index for betweenness: 20±16, fisher

exact test, h=1 for 12/21 patients). Other centrality measures had a varied range of associations with high spiking electrodes. We also repeated the tests at 50 percentile threshold had noticed similar results.

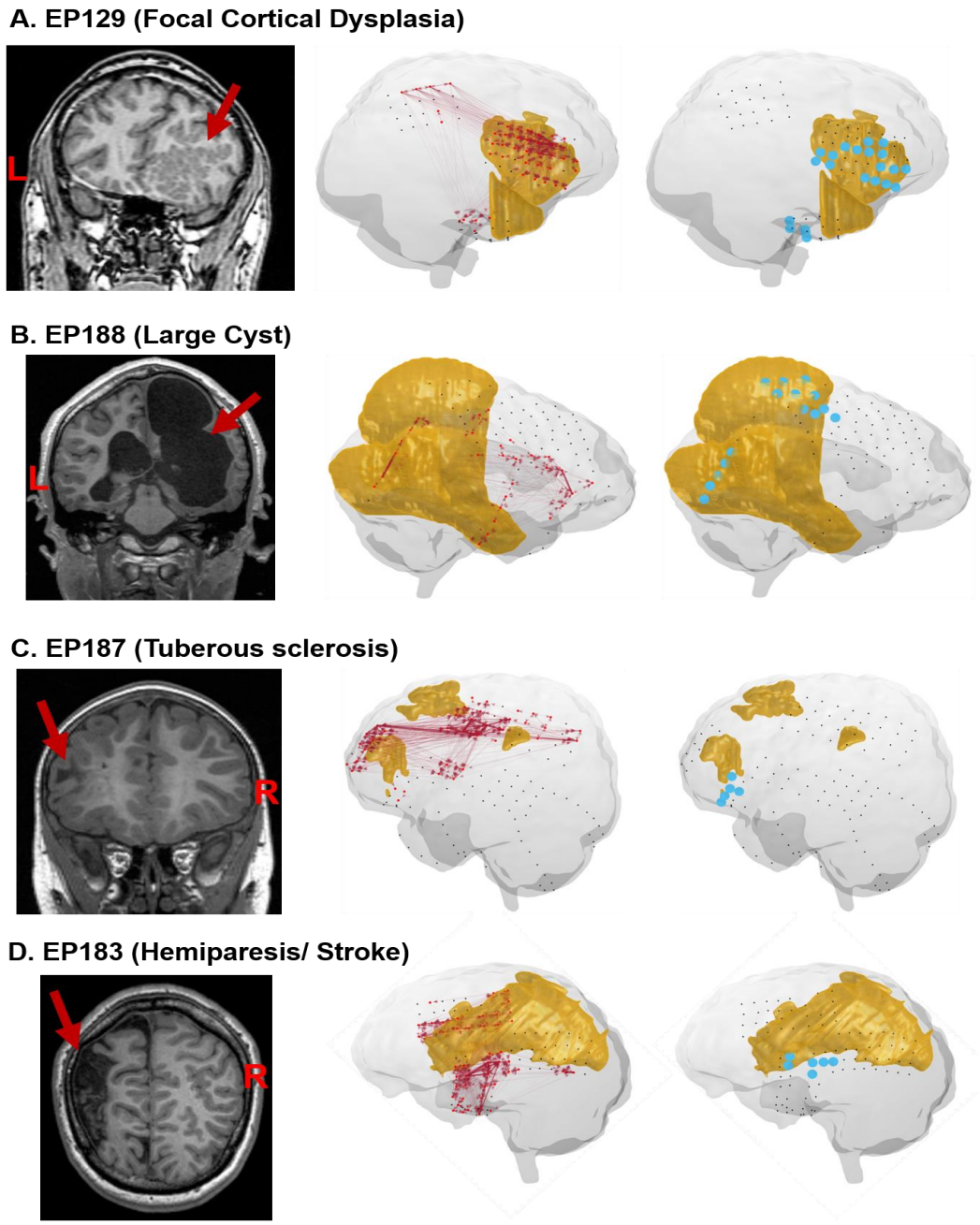


Figure 6.3. Spike propagations reverberates on or adjacent to lesion location. (A) Case of focal cortical dysplasia where spike network reverberates on the lesion and seizure onset is also observed in the same area along with a few electrode locations on the temporal lobe. (B), (C) and (D) shows three different lesional cases with Large Cyst, TSC and Stroke respectively where the spike network reverberated in peri-lesional regions. The seizure onset (cyan color) and the spike network did not align exactly, but the SOZ electrodes are near the lesion.

6.4. Discussion

We evaluated the interictal spike propagation using causality based dDTF and explored the propagation pattern of interictal spikes in 23 neocortical cases. We further evaluated the relationship between spike propagation, seizure onset, and lesion location. Interictal spike propagations were highly reproducible yet unique in all patients as previously revealed (Biswajit Maharathi et al. 2018), suggesting interictal spikes are 'hard-wired' and can potentially represent the underlying active epileptic network. While spike network was significantly consistent in most patients, patient EP122 and EP201 did not have a reproducible network. EP122 had significantly low spike count, often scattered, which might be the reason for the network inconsistency.

We compared seizure onset electrodes and the spike propagation centrality measures. As previously observed, for 11 out of 21 patients, the seizure onset was significantly associated with any centrality measures (B. Maharathi, Loeb, and Patton 2019), indicating we can use any of the centrality measures from spike propagation to predict seizure onset regions in such patients. While hub centrality was the best measure predicting SOZ in 14 of 21 patients, betweenness was the worst measure and only predicted seizure onset in 9 of 21 patients. The simple spike count was also a good measure to predict SOZ. High spiking electrodes in the current patient cohort could predict SOZ in 11 patients accurately. Surprising, the patients in which the centrality measures were not well associated with SOZ are the patients with lesion or abnormalities, as observed on MRI. Such mismatch might suggest that while non-lesional patients have higher chances of spike and seizure onset generating from the adjacent cortical regions, lesion influences these events in lesional patients. In lesional cases, only a part of the spike network aligned with the seizure onset region, suggesting that while some of the spiking regions might have the same origin as the seizures, lesions have additional pathological regions with an active epileptic network, primarily near the edge of the lesion.

We evaluated the relationship between the spike count at each electrode location and different spike propagation centrality measures. PageRank centrality and high spiking electrodes were significantly aligned. The PageRank centrality measures how often the node is getting connected from other nodes and represents the relative importance of nodes in a network. The high concordance of frequent spiking

electrodes with PageRank centrality suggests that these electrodes receive propagations from several other electrodes or are connected with electrodes that receive several other connections from different electrodes. The high spiking electrodes have previously been associated with the seizure onset regions and hypothesized to play a significant role in epilepsy. The PageRank centrality might be representing significant propagation receiving property of the spikes. These high spiking electrodes also frequently co-localized with hub centrality. Hubs are the nodes that have higher direct outgoing connectivity with other nodes as compared to the average outgoing connections. The concordance of high spiking electrodes with spike propagations hubs might suggest that the frequent spiking electrodes often connect to several cortical regions and initiate connections to multiple electrodes when they spike. The frequent propagation activity of high spiking electrodes and their concordance with seizure onset electrodes might suggest that they have a significant role in fortifying the epileptic network in non-lesional patients. They might be playing a similar role in patients with lesions, but lesion might generate additional spike activities.

The current study comes with several limitations: patient cohort size, diversity of pathology, and lack of additional data modalities, however the primary focus of the study was to establish relationship between spike propagation, seizure onset, and any existing lesion as identified on MRI. The present analysis provides apparent evidence of spike propagation patterns and its relationship with seizure onset in both lesional and non-lesional cases. Our results show that while non-lesional patients have a reproducible spike network that aligns with the seizure onset, the results differ in the patients with a lesion. In the lesional patients, the seizure onset is partially localized with the spike centrality measures and frequent spiking electrodes suggesting additional pathological active regions are present which distinct form seizure regions are. Further studies are necessary to establish a stronger relationship between spikes and seizures. However, these measured networks have good potential to assist in surgical planning and targeted drug development.

VII. GENERAL DISCUSSION

The dissertation work explored the causal propagation of time-locked interictal spikes in the human neocortex and related it to the brain topography and lesion. The work also revealed the relationship between seizure onset zones (SOZ), interictal spike propagation network properties, and brain lesions if present. While revealing the basic functioning of the interictal spikes in the pathological epileptic brain, the dissertation takes forward our scientific understanding of the complex coordinated information flow of these paroxysmal events in the human brain and provides an edge to explore its utilization in clinical settings.

7.1. Contributions to Neuroscience

The current work established that the interictal spike network is consistent within each patient, specifically it is reproducible at different time points and across frequency bands. These spike networks were reproducible when we considered all the electrodes placed on the brain or only a subset of it. Lesions or SOZ did not significantly alter the reproducibility of these networks. However, we observed that the network consistency between SOZ and non-SOZ electrodes in non-lesional patients was significant. Each patient had a unique spike propagation pattern. On the temporal lobe from electrodes placed through the Foramen Ovale of the skull, interictal spikes propagated in multiple directions and often crossed to the contralateral temporal lobe, mostly from and to posterior positions. In all our analyses, we used subdural electrodes, placed close to the cortical surface. Such electrodes in the temporal lobe recorded considerably more epileptic activity than scalp electrodes, which often detected very few events.

The question of whether there is a relationship between interictal spikes and SOZ is crucial to the field, but not straight forward. Seizure onset did not directly correlate with high spiking electrode regions for all patients, as previously thought (K. J. Staley, White, and Dudek 2011). Spike events are perhaps not as vital as if and how they propagate. In patients without any lesion, seizure onset was predicted by any of the spike propagation centrality measures, even with simple spike count. However, there was no exact concordance between spike network and seizure onset in patients with a lesion. Overall, these seizure onset zones were best associated with interictal spike hubs.

The presence of a lesion on the neocortex or temporal lobe did have a significant effect on spike propagation. When lesions were present on the temporal lobe, most of the spike propagation was reverberating pairs in perilesional positions and did not cross to the contralateral side. In these patients, the seizure onset aligned with a smaller cluster of reverberating spikes. In patients with a lesion on the neocortex, the relationship between spike network and seizure onset was similar to that observed on the temporal lobe. Interictal spikes were observed on and around lesions, but also far from lesions. A subset of spiking electrodes around the lesion form a reverberating pair, and a subset of these electrodes often associated seizure onset electrodes. However, similar reverberating propagations were also observed in distant cortical regions. The lesions are hypothesized to infiltrate the perilesional space, in which case they might induce anomalous propagations. Only some of those regions might generate enough abnormal excitation to make the tissue prone to seizure activity.

All spikes did not propagate. In multiple studies, we revealed that only 70-85% of the spikes were propagating across different cortical regions. Spike occurrence was not uniform across all electrodes; there were high spike occurrence electrodes and comparably low spiking electrodes. These high spiking electrodes were not the regions that initiate most propagations; instead, high spiking electrodes often received propagations from other regions. These high spiking electrodes did have higher relative importance in terms of PageRank centrality measure of the interictal spike network, suggesting these high spiking electrodes either received propagations from several other spiking electrodes or connected with electrodes which received several propagations within each spike block. A subset of these high spiking regions also acted as network hubs meaning they initiated propagations to multiple electrodes when analyzed within each spike block. These hubs were also associated with seizure onset zones (SOZ).

Spike propagations were related to the natural topography of the brain surface. This may be a representation of the idea of “hard-wired” circuits, with closer connections having more traffic. With increasing geodesic distance, the propagations decreased between a pair of electrodes, and propagation count was significantly reduced while crossing large sulcal structures like the central sulcus.

Interictal spikes blocks, which were isolated time epochs, does not represent the entire brain activity. We took the entire ECoG signal recorded, evaluated the total network, and compared it with the interictal

spike network. The total network, which was also very consistent, had more propagations than interictal spike propagation, and did not have any similarity to the interictal spike network. When we investigated these two networks at different frequency bands, the interictal spike network was always a better predictor of seizure onset zones than the total network. While the spike network could predict the seizure onset at any frequency band, the total network could best predict seizure onset zones at high-frequency oscillations, which was still less accurate than the interictal spike network. Interestingly, the total network also gets affected because of the brain topography, but the effect is not as dramatic compared to the spike network.

The current thesis work reveals the neuroscience of pathologic brain connectivity and provides important clinical information regarding the epileptic activity of the patient's brain. Clinically interictal spikes have a significant role in epileptogenesis, as suggested by previous studies. However, the current work reveals the critical brain locations among the spiking electrodes and reveals the electrode location that generates seizures.

Interictal spikes and high-frequency oscillations are the two epileptic electrophysiological biomarkers extensively studied to predict the seizure onset zones in clinical settings. Both events are associated with accurate SOZ prediction and good surgical outcomes after the corresponding tissue resection. However, when these HFOs are co-determined with interictal spikes, the results are much better. The current challenges in the HFO research specifically isolate the pathological HFOs from the physiological ones, may suggest that the interictal spikes might be a better biomarker to predict the SOZ and use in a clinical setting. While frequent spiking regions are often associated with seizure onset zones, the current work suggests that the spike network centrality measures might pinpoint the specific locations and help optimize the surgical planning to minimize tissue removal. Resection may not be the most suitable strategy. It may so happen that spike onset regions' isolation may solve the spread of the epileptic network. We might have to separate the spiking regions active in propagation from the other regions.

7.2. Contributions to Neural Engineering

Several novel network analysis modules enabled a pipeline for better understanding of the propagation of interictal spikes. The first module was that we isolated time epochs of the interictal spike propagations (called the *spike network)* led to better predictions of seizure onset zones (SOZ) than using the entire stretch

of times (called the *total network).* Isolating the time segments of relevant interictal spike activity helped pinpoint epilepsy-related network activity from the rest. While several studies have been conducted on the total network, preictal and ictal times (Li et al. 2016; Wilke et al. 2010; Hur and Kim 2015), to our knowledge, we were first to this initial isolation of only the times of interictal spike propagations (B. Maharathi, Loeb, and Patton 2019; Biswajit Maharathi et al. 2018). This may be simply the case of having more signal available to drive strong conclusions.

The second module enabled frequency isolation. Using this, we found time-isolated interictal spike network propagations were consistent across frequency. While we did not find significant differences across frequencies, it may be a tool for future analyses that might need isolated frequency. For all times (total network), SOZ were predicted by high-frequency oscillations range (80-250 Hz), which is comparable to others' findings who did not time-isolate (J. Jacobs et al. 2008; Modur and Miocinovic 2015).

Another important module was the phase-randomized surrogate data thresholds in dDTF network evaluations. Although dDTF evaluates the propagation, it needs a thresholding to detect events. Surrogate data as previously recommended (Faes et al. 2004; Theiler and Prichard 1997; Junfeng Sun, Xiangfei Hong, and Shanbao Tong 2012) helps statistically validated the correctness of these events above background noise. Since dDTF is very sensitive to phase, the use of phase-randomized approaches helped best detect output.

Another important module was the centrality measures from graph theory, which helped understand the way interictal spikes propagate. We gained insight on the network's bulk behavior and the many ways propagations can occur. Centrality measures revealed the importance of different electrodes positions and helped find associations between interictal spiking, SOZ and lesion location. Previous research suggested *betweenness* (Wilke, Worrell, and He 2011), *indegree* (Li et al. 2016), and *outdegree* (Haneef and Chiang 2014) best predict SOZ. We discovered these properties were patient-dependent, and while many centrality measures could predict the SOZ in a subset of patients, but hub centrality was the best predictor of SOZ across all patients. This suggests electrodes initiating simultaneous propagations are more prone to be related to SOZ. Interestingly, we found that betweenness was not a good predictor of SOZ. Graph centrality estimating SOZ might be dependent on the method used to get the network.

Finally, we developed a module related functional networks evaluated from EEG with brain structures and topology. We evaluated the change in propagation count with increasing distance between electrodes. While Euclidean distance measures the shortest distance between two points as if they are connected through a straight line, human brain follows a convoluted structure that includes gyri and sulci. We calculated the geodesic distance between electrode points that calculates the true shortest distance between electrodes through the sulcal folding and is a better measure than Euclidean distances. The work revealed the exponential decreasing propagation count with increasing electrode geodesic distance and helped us understand that central sulcus like large sulci act as barrier to propagation. The effect of decreasing propagation count vs distance was not so drastic in total network.

7.3. Limitations of the work

7.3.1. Patient Selection

Epilepsy differs from other neurological disorders due to its heterogeneity in etiology and phenotypes. The biggest issue with this study was the patient selection. Our patient cohort came from different age groups (pediatric and adult), different epilepsy duration, and electrodes were placed on different brain locations. The patients had different brain conditions ranging from polymicrogyria, stroke, tuberous sclerosis, atrophy, and many patients did not have any identifiable lesion on their brain through MRI. These patients also had different seizure semiology, some patients had focal seizures, and pediatric cases often had epileptic spasms. Interestingly, these patients also had unique epileptic networks, which made comparisons across patients infeasible.

7.3.2. Electrode coverage and spatial resolution

Epilepsy surgery often focuses on a minimally invasive procedure that can have optimum outcomes, and the primary focus remains to remove the seizure onset region. In the presence of a lesion, the goal also includes removing the lesion completely. In such a situation, the electrodes only implanted as required. While such electrode placements are best for the patient, it limits the research scope by limiting the area of coverage. With limited data modalities and only a part of the brain covered with electrodes, we are restricted to analyze a biased brain region. Intraoperative electrodes are not placed on the whole brain, limiting our understanding of the events that occur on the brain's contralateral side, which is presumed to normal. In

the current dissertation, all patients had subdural electrode placement. While the information collected from the neocortex provided excellent information on the spatial-temporal propagation of epileptic events, we could not explore the propagation activities that occur at deeper brain layers and through the white matter cortex. Suppose we would have access to higher spatial resolution data set. In that case, we could precisely map the exact pathway of information propagation and explore the different intricate brain regions involved in the epileptic network.

7.3.3. Methodology limitations

There are several methods developed to understand brain networks. While each algorithm has its purpose, the dDTF was developed based on the Grainger causality framework to understand the signal propagation between a pair of electrodes in the presence of many electrodes. While the algorithm performed well and claimed to be accurate, it still needs statistical validation. The validation process is too time-consuming and needs massive computing resources. Alternative methods should be explored that provide similar or better estimations but less computational heavy and executes in a shorter time. Also, these algorithms need enough data to generate the multivariate autoregressive models. In the case of limited data availability, alternative non-parametric methods should be explored.

7.4. Future visions

Our patient cohort consisted of only 30 minutes of information extracted from several days of intraoperative monitoring with limited electrode coverage on the cortical surface and no depth electrodes. The data analyzed in the current dissertation is also limited to EEG and MRI modalities. There are several scopes of improvement and with better data collection, intricate scientific details can be revealed.

A few minutes of EEG data is often sufficient to understand the pathological network, however it does not provide any information on the temporal evolution the disease. It would be exciting to see how this interictal spike evolves over longer period, and its variation with the circadian rhythm. Moreover, anti-epileptic drugs are known to suppress epileptic events. It would be exciting to investigate the total network and spike network before discontinuing the drug and compare it with after the drug is withdrawn.

The other aspect is the temporal evolution of the network. Epilepsy is a network disease, and this network evolves. While the disease network's temporal progression is difficult to track in human cases, similar experiments should be conducted in animal models of epilepsy. This will provide us with a better understanding of interictal spikes and seizures' network evolution to help develop targeted drug development and intervention strategy.

While the current study, with available ECoG and MRI, does a surprisingly good job identifying the epileptic network and relating it to the underlying natural brain topography and pathological lesions, it is still limited to the neocortex. Integration of other data modalities such as DTI/DWI should be strongly considered to delineate the correlation between functional network recorded from the brain's surface and white matter tract. This will provide a comprehensive understanding of the structural-functional dynamics of the epileptic network.

One can easily envision a better world if one recognizes the recent evolution of new electrode technology and the possibility of very dense networks. Epilepsy has frequent pathological activities in the inner layers of the cortex and mesial structures. With the limitation of grid electrodes on the neocortex, it is impossible to collect high-resolution spatial-temporal information from those structures. With the advancement of microelectrodes, it is possible to implant several stereotactic depth electrodes on deeper brain structures for better data collection. This will be immensely helpful in the presence of a lesion. With adequate electrode implantation, we can understand the neural abnormalities on the lesion's surrounding tissue, which often involves deeper layers of the neocortex and white matter tracks.

The electrical recordings observed on the neocortex are the implication of the synchronous firing of several million neurons under the recording electrode. This neural activation is not random; instead, it follows specific molecular pathway activation. Previous studies have described decreased in GABA receptors and increase in postsynaptic glutamate receptors in epileptogenic tissue (K. M. Jacobs, Kharazia, and Prince 1999). Recent studies have reported that the epileptic tissue shows the presence of micro lesions in the deeper cortical layers with decreased neuronal processes and MAPK/CREB activation (Dachet et al. 2015). On the genetic alteration level, hyper excitable states, as seen in epilepsy, are also associated with long non-coding RNA activity (Barry et al. 2017). It would be interesting to see the system

biology studies on these epileptic activities that integrate the molecular, cellular, structural, and functional activity of epilepsy related activities. A better understanding of such end-to-end mechanisms will help future drug discovery directions and other therapeutic interventions.

7.5. Conclusion

Despite the limitations, the current study is the first of its kind that provides a comprehensive analysis of the interictal spike network in the epileptic neocortex and its relationship to brain topography, presence of lesions, and seizure onset zones. The analyses reveal the consistent propagation of interictal spikes across multiple days and frequency bands, unique to each patient. Since the ten-minute time intervals were sufficient to find the reproducible network, this might reduce the time any patient has to go through monitoring during intraoperative surgery. Moreover, the interictal spike network was reproducible at different frequency bands, including high-frequency oscillations suggesting we might reliably predict the spiking network by evaluating it at lower frequency narrow bands.

The interictal spike network is partially localized with seizure onset, suggesting the two are not directly correlated. In contrast, a subset of spikes may come from the same region as seizures. The interictal spikes might have broader control over the epileptic network and may create additional onset zones distinct from the already identified ones. Along with removing the seizure onset zones, it might be useful to focus on these network active spiking regions for better patient outcomes.

Frequent spiking electrodes also revealed brain lesions' role in generating additional tissue regions prone to generate interictal spikes that are not associated with seizure onset zones. While the work's clinical implication is still in the preliminary stage and needs additional work, these networks may help develop targeted drugs and surgical planning. They also help us understand the basic network functioning of the pathologic brain.

All the patients analyzed here were suitable surgical candidates with intracranial monitoring. While network analysis in such cases helps us better understand the pathological network, we can also use such analysis in other applications such as electrical stimulation and magnetic stimulation, where accurate identification of the seizure onset locations is essential.

While the fully developed clinical application of such analyses is yet to be discovered, the current work sheds light on pathological brain activity and its unique characteristics compared to normal physiological brain activity. Additional work in a similar direction will help us understand the complex dynamics of the different neural assemblies of the normal brain and the pathological alteration in conditions such as epilepsy.

VIII. APPENDIX I

UNIVERSITY OF ILLINOIS
AT CHICAGO

Office for the Protection of Research Subjects (OPRS)
Office of the Vice Chancellor for Research (MC 672)
203 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227

Exemption Granted

September 9, 2015

Jeffrey Loeb, MD
Neurology
912 S. Wood St.
NPI North Bldg. Rm 657, M/C 796
Chicago, IL 60612
Phone: (312) 996-1757 / Fax: (312) 996-4169

RE: Research Protocol # 2015-0878
"MAPK Signaling in Neocortical Epilepsy"

PAF#:	**2015-03680**
Grant/Contract No:	**NIH 1 R56 NS083527-01A1**
Grant/Contract Title:	**MAPK Signaling in Neocortical Epilepsy**
Sponsors:	**National Institute of Health (NIH)**
Exemption Period:	**September 9, 2015 – September 8, 2018**
Subject Enrollment #:	200 (existing samples/data)
Performance Site:	UIC

Dear Dr. Loeb:

Your Initial Review (Expedited) submission was reviewed on September 9, 2015 and it was determined that your research protocol meets the criteria for exemption as defined in the U. S. Department of Health and Human Services Regulations for the Protection of Human Subjects [(45 CFR 46.101(b)]. You may now begin your research.

The specific exemption category under 45 CFR 46.101(b) is:

(4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

The minimal identifiable elements included with the data (ZIP code and month/year of birth) are allowable under exempt category 4 as a Limited Data Set. Since consent/authorization were obtained at the time of the original sample/data collection in accordance with the Wayne State University IRB approval, additional consent/authorization waivers are not required at this time.

Please note that the research cannot begin until the Materials Transfer Agreement (MTA) with Wayne State University has been executed. Additionally, Animal Care Committee (ACC) approval is required prior to initiation of any of the animal model studies outlined in the protocol.

You are reminded that investigators whose research involving human subjects is determined to be exempt from the federal regulations for the protection of human subjects still have responsibilities for the ethical conduct of the research under state law and UIC policy. Please be aware of the following UIC policies and responsibilities for investigators:

1. Amendments You are responsible for reporting any amendments to your research protocol that may affect the determination of the exemption and may result in your research no longer being eligible for the exemption that has been granted.

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3. Final Report When you have completed work on your research protocol, you should submit a final report to the Office for Protection of Research Subjects (OPRS).

Please be sure to:

→Use your research protocol number (#2015-0878) on any documents or correspondence with the IRB concerning your research protocol.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact me at (312) 413-3202 or the OPRS office at (312) 996-1711. Please send any correspondence about this protocol to OPRS at 203 AOB, M/C 672.

Sincerely,

Teresa D. Johnston, B.S., C.I.P.
Assistant Director
Office for the Protection of Research Subjects

cc: Larry Tobacman, Senior Associate Dean for Research, College of Medicine, M/C 784
OVCR Administration, M/C 672

Exemption Granted

January 30, 2020

Anna Serafini, MD
Neurology
Phone: (312) 413-8114

RE: **Protocol # 2020-0030**
"Ictal and interictal hippocampal communication in epileptic patients with foramen ovale electrodes"

Dear Anna Serafini:

Your Claim of exemption was reviewed on **January 30, 2020** and it was determined that your research meets the criteria for exemption as defined in the U.S. Department of Health and Human Services Regulations for the Protection of Human Subjects [45 CFR 46.104(d)]. You may now begin your research.

Exemption Granted Date: January 30, 2020
Sponsor: None

The specific exemption category under 45 CFR 46.104(d) is: 4

HIPAA Waiver:
A waiver of HIPAA Authorization has been granted [45 CFR 164.512(i)(1)(i)] for the use of protected health information (PHI) for research purposes. Please note that this research has been determined to meet the criteria for exemption under category 4. Under the revised Common Rule regulations (2018 Requirements, effective January 21, 2019), research involving secondary analysis of UIC medical records data qualifies for exempt category 4 when the research is limited to the collection and analysis of UIC protected health information within the UIC covered entity per HIPAA. The exemption does not apply to the research use of PHI from non-UIC entities, or to research that involves disclosure of UIC PHI outside of the UIC covered entity. Any future plans to disclose PHI outside of the UIC covered entity will require a protocol amendment and re-review by the IRB.

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(HSPP) and the guidance ***Investigator Responsibilities***.

We wish you the best as you conduct your research. If you have any questions or need further help, please contact me at (312) 355-2908 or the OPRS office at (312) 996-1711. Please send any correspondence about this protocol to OPRS via OPRS Live.

Sincerely,
Charles W. Hoehne, B.S., C.I.P.
Assistant Director, IRB #7
Office for the Protection of Research Subjects

cc: Jeffrey A. Loeb, Neurology

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Zou, Guangyu, Jing Hua, Xianfeng Gu, and Otto Muzik. 2006. “An Approach for Intersubject Analysis of 3D Brain Images Based on Conformal Geometry.” In *2006 International Conference on Image Processing*, 1193–96. IEEE. https://doi.org/10.1109/ICIP.2006.312697.

VITA

EDUCATION

2016-present University of Illinois at Chicago, IL, USA

Ph.D. candidate, Bioengineering

2013-2015 University of Illinois at Chicago, IL, USA

M.S., Bioengineering

2007-2011 National Institute of Technology at Rourkela, INDIA

Bachelor of Technology, Biotechnology and Medical Engineering

RESEARCH AND WORK EXPERIENCE

2014-present **Intuition: Novel framework for medical information processing**

Design and development of an advanced database structure that holds multi-dimensional patient clinical and research information including EEG, MRI, histology and Genomics with intuitive user interface and data sharing capability.

2014-present **Dynamic functional network of Epileptic events**
Discovered the epileptic spike functional network and its importance in clinical care and surgical planning; Designed and developed program for automatic detection of epileptic EEG events (spike, seizure, artefacts) in animal model of Epilepsy; Designed a multi-stage & multivariate data analytic framework in MATLAB for measuring causal interaction of epileptic EEG events in Human and animal epileptic data with improved precision and reproducibility; Discovered the relationship between edema volume with seizure occurrence in Neurocysticercosis patients using computational Image analysis and machine learning classification.; Discovered the role of hippocampal functional network with epileptic seizures in temporal lobe epilepsy.
(Advisor: James L. Patton, PhD, Jeffrey A. Loeb)

2011-2013 **QA analyst in healthcare domain for AETNA, USA**, Infosys Ltd., India
Worked on development and testing of 11 application related to predictive modeling; Performed Testing (black box, white box, sanity testing, UAT, Regression) for predictive modeling systems; Subject matter expert on ICD9, ICD10, Rx, CPT and Loin codes.

2010-2010 **Summer Research Intern,** Advanced Enzyme Ltd., India
Developed computational models to analyze the enhancement of enzyme production from different bacterial strains; Worked on scheduled plant visits to monitor the quality of production.

2009-2009 **Summer Research Associate,** NIT Rourkela, India
Worked on comparative study on the performance behavior of different phenol-degrading bacteria to identify and habituate superior strains for efficient degradation of phenolic industrial waste; Designed and tested large bioreactors for industrial implementation for phenolic waste management.

PROFESSIONAL MEMBERSHIP AND SERVICES

2014 – current IEEE EMBC member
2016 – current Reviewer for IEEE EMBC Conference
2019 – current Workgroup member of IEEE Standards (IEEE P2733 Clinical IoT DDI with TIPPSS)
2020 – current Reviewer AMIA Annual Symposium

HONORS

2020 2020 AES Fellow
2018 Mary Brazier Young Investigator Paper Award (International Federation of Clinical Neurophysiology)
2018 CCTS Multidisciplinary Team Science Award
2018 UI-College of Medicine research Award (Honorary mention)
2020 Chancellor's Student Service and Leadership Award
2019 Graduate College presentation travel award
2019 Graduate student Council travel award
2019 Chancellor's Student Service and Leadership Award
2018 Chancellor's Student Service and Leadership Award
2017 Outstanding Contribution award from Graduate Student Council (GSC)
2016 Graduate College presentation travel award
2016 Graduate student Council travel award

LEADERSHIP

2019-2020 Vice-President, Graduate Student Council
2019-2020 Student member to the Senate Executive committee
2018-2019 Representative to the Research Committee of Information technology Governance Council, UIC.
2017-2019 Student member to the UIC senate and senate committees.
2017-2019 Primary department representative (Bioengineering) to Graduate Student Council, UIC.
2017-2019 Executive Committee member of Graduate Student Council, UIC.

PUBLICATIONS

PEER REVIEWED MANUSCRIPTS

2020 **Maharathi B**., Eugene M. Sadhu, Jeffrey A. Loeb (2020). Intuition: Integration of Multimodal Datasets in Human Epilepsy for Clinical Care and Discovery. (Manuscript submitted)

2020 Biswajit Maharathi, James Patton, Anna Serafini, Konstantin Slavin, Jeffrey A. Loeb (2020). Highly consistent interictal spike networks in temporal lobe epilepsy. (Manuscript submitted)

2020 Joseph R. Geraghty, Danielle Senador, **Biswajit Maharathi**, Mitchell P. Butler, Deepshika Sudhakar, Rachael A. Smith, Yichao Wu, Jeffrey A. Loeb (2020). Modulation of locomotive behaviors by location-specific epileptic spiking and seizures. (Manuscript submitted)

2019 Cho, S., **Maharathi, B.**, Ball, K. L., Loeb, J. A., & Pevsner, J. (2019). Sturge-Weber Syndrome Patient Registry: Delayed Diagnosis and Poor Seizure Control. The Journal of pediatrics. https://doi.org/10.1016/j.jpeds.2019.08.025

2019 **Maharathi, B.,** Loeb, J. A., & Patton, J. (2019). Central sulcus is a barrier to causal propagation in epileptic networks. In 2019 41st Annual International Conference of the IEEE Engineering in

Medicine and Biology Society (EMBC) (pp. 2555–2559). IEEE. https://doi.org/10.1109/EMBC.2019.8857401

2019 **Maharathi, B.**, Loeb, J. A., & Patton, J. (2019, March). Epileptic spike functional networks best predict seizure onset zones. In 2019 9th International IEEE/EMBS Conference on Neural Engineering (NER) (pp. 895-898). IEEE. http://ieeexplore.ieee.org/stamp/stamp.jsp?tp=&arnumber=8717090&isnumber=8716881

2018 **Maharathi, B.,** Wlodarski, R., Bagla, S., Asano, E., Hua, J., Patton, J., & Loeb, J. A. (2018). Interictal spike connectivity in human epileptic neocortex. Clinical Neurophysiology. https://doi.org/10.1016/j.clinph.2018.11.025

(Cover page illustration and Editor's choice article)

2018 Herrick, J. A., **Maharathi, B.**, Kim, J. S., Abundis, G. G., Garg, A., Gonzales, I., … Loeb, J. A. (2018). Inflammation is a key risk factor for persistent seizures in neurocysticercosis. Annals of Clinical and Translational Neurology. https://doi.org/10.1002/acn3.562

2016 **Maharathi, B.**, Loeb, J. A., & Patton, J. (2016). Estimation of resting state effective connectivity in epilepsy using direct-directed transfer function. In 2016 38th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. (Vol. 2016–Octob, pp. 716–719). IEEE. https://doi.org/10.1109/EMBC.2016.7590802

OTHER PUBLICATIONS

2018 **Biswajit Maharathi**. "Understanding Epilepsy: Big Data Way" In Neurology & Rehabilitation Newsletter, winter 2018; https://chicago.medicine.uic.edu/understanding-epilepsy-big-data-way/ .

POSTER AND PAPER PRESENTATIONS

2019 **Maharathi, B**, Loeb, J. A., & Patton, J.; "Interictal spike connectivity in human epileptic neocortex" at MATTER AI & Neurosciences Summit (The AI approach to classic statistical methods)

2019 **Maharathi, B.,** Loeb, J. A., & Patton, J.; "Central sulcus is a barrier to causal propagation in epileptic networks" at EMBC 2019

2019 **Maharathi, B.**, Loeb, J. A., & Patton, J.; "Epileptic spike functional networks best predict seizure onset zones" at NER 2019

2018 **Maharathi, B**, Loeb, J. A., & Patton, J.; "Interictal spike connectivity in human epileptic neocortex" at UIC COM Research day, 2018

2018 Joseph R. Geraghty, **Biswajit Maharathi**, Abdullah Muhammad, Haoliang Xu,M.D., Jeffrey A. Loeb,M.D.,Ph.D., Fernando D. Testai , M.D., Ph.D. "Early brain injury after subarachnoid hemorrhage and its potential role in epileptogenesis: animal models and therapeutic applications" In ISC-2018.

2017 Herrick, Jesica A., Anjali Garg, Jin Suh Kim, **Biswajit Maharathi**, Gerardo Gomez Abundis, Isidro Gonzales, Herbert Saavedra, Javier Bustos, Hector H. Garcia, and Jeffery A. Loeb. "Inflammation Is A Key Risk Factor For Refractory Seizures In Patients With Neurocysticercosis." In American Journal Of Tropical Medicine And Hygiene, Vol. 97, No. 5, Pp. 11-11. 8000 Westpark Dr, Ste 130, Mclean, Va 22101 Usa: Amer Soc Trop Med & Hygiene, 2017

2016 **Maharathi, B**, Loeb, J. A., & Patton, J.; "Estimation of resting state effective connectivity in epilepsy using direct-directed transfer function"; 38th Annu. Int. Conf. IEEE Eng. Med. Biol. Soc., 2016

2011 Nayak BP and **Maharathi B**; “Design of non-invasive fatigue detection device and its validation”; World Congress on Biotechnology (WCB-2011), Hyderabad

2010 Nayak BP, Routray A, Satpathy GR and **Maharathi B**; “Detecting the Genesis of Fatigue in Trained Drivers by Studying the Variation of Blood Biochemical Parameters under Simulated Driving Condition”; International Conference on Biological Sciences and Engineering (ICBSE-2010), Hyderabad.

FUNDING SUPPORT

2019-2020 CCTS Pre-doctoral Education for Clinical and Translational Scientists (PECTS) Fellowship

2018-2019 **Co-Investigated** NIH U54NS065705-09 Pilot Project, Brain Vascular Malformation Consortium Developing a multicenter, integrated data, tissue, genomics, and imaging repository for Sturge-Weber Syndrome, PI: J Loeb $62,000