PAIRWISE GRANGER CAUSALITY FINDINGS IN PATIENTS WITH PARTIAL EPILEPSY REFRACTORY TO MEDICAL TREATMENT

By

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To my wife, Lida Esperanza and our children, Valerie, David and Nicholas, and to all patients affected with epilepsy

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AED	anti-epileptic drug
ANOVA	analysis of variance
APPCI	Advanced Postgraduate Program in Clinical Investigation
BMRI	brain magnetic resonance imaging
CNS	central nervous system
EMU	Epilepsy Monitoring Unit
EN	epileptogenic network
GABA	gama-amino butyric acid
HS	hippocampus sclerosis
ILAE	International League Against Epilepsy
IN	ictogenic network
IO	ictal onset
IRB	Institutional Review Board
ISAP	intra-carotid sodium amobarbital procedure
IZ	ictal zone
LS	limbic system
MEG	magneto-encephalogram
MLTN	mesio-limbic-temporal network
NT	neurotransmitters
PCS	partial complex seizures
PERT	partial epilepsy refractory to medical treatment
PET	positron emission tomography
PGC	pairwise Granger causality
PNS	peripheral nervous system

ROI	region of interest
SD	standard deviation
SPECT	single photon emission computed tomography
STN	signal to noise ratio
TLE	temporal lobe epilepsy
VEEG	video electroencephalogram
WM	white matter

Abstract of Thesis Presented to the Graduate School
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Based on the association between ictal onset (IO) and a neuronal network,[1-6] we tested the hypothesis that the ictal zone (IZ) in patients with partial epilepsy refractory to medical treatment (PERT) originates in a single network and propagates to the contra-lateral hemisphere (inter-hemispheric theory) as opposed to no contra-lateral ictal propagation (intra-hemispheric) using Linear Pairwise Granger Causality (PGC) analysis of interictal and ictal EEG recordings in a case series study. Hence, we prospectively studied ninety partial complex seizures (PCS) in twenty-three subjects and defined seizure directionality in involved neuronal networks and compared to non-involved control neuronal networks. The EEG raw data were analyzed using linear PGC. Boot-strapping methodologies were used to address the statistical significance of the network interactions defined with PGC. Time frequency distribution was plotted for each seizure and compared versus controls.

PGC was statistically significant for intra-hemispheric directionality if the IO was over the right temporal lobe (p=0.0257) and for inter-hemispheric directionality if the IO was over the left frontal lobe (p=0.0028). PGC showed a trend for a significant intra-hemispheric directionality if the IO was over the left temporal (p=0.0548) and right

frontal lobe (p=0.0558). Furthermore, there were no significant differences when looking at the inter-hemispheric PGC measures obtained in subjects with seizures with an IO over the left frontal (p=0.2882), left temporal (p=0.1572), right frontal (p=0.6772) and right temporal networks (p=0.7795) when compared against the parietal network. The possible explanations of this last finding are at least three-fold: 1) There is in fact no contra-lateral ictal propagation,[7] 2) contra-lateral ictal propagation is not identifiable with PGC, and/or 3) The “hidden element” theory may apply, that is, the causal relation of two neurons can be affected by the effects of a third neuron that is not measured.[8] Although this study has several limitations, the findings will serve as a principle for the development of models capable of predicting seizure directionality and for further evaluation of established methodologies such as segmentation and surrogate analysis.

CHAPTER 1
INTRODUCTION

Background

Epilepsy represents the most common neurological disorder worldwide, with an estimated 0.5-1% prevalence, comprising approximately 60 million cases.[9] Most epilepsy syndromes are outgrown by teenage years or respond well to anti-epileptic drugs (AED). However, a subset of patients with epilepsy and a focal ictal zone (IZ) do not respond to conventional AED. This population may qualify for a surgical resection if the IZ is well defined. Our understanding of epileptogenic mechanisms has improved due to electrophysiological and neuro-imaging evidence documenting a network of neurons involved during an ictal event.[6] Such evidence includes scalp and intracranial video-electroencephalographic (VEEG) recordings, brain magnetic resonance imaging (BMRI), single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies.[6] There is a growing interest for using other non-invasive tools in the analysis of real-time and in-vivo EEG data to define the ictogenic network (IN).[8, 10, 4, 11] Thus, Pairwise Granger Causality (PGC), an effective connectivity measure analysis tool based on an autoregressive model used to investigate directional interactions between two time series, has been borrowed from the economy field to apply in to the prediction of seizure activity. Our seizure prediction research study was possible due to multi-disciplinary collaborations of clinicians, neuroscientists and bio-statisticians. Our team leadership has developed a program project aiming to better understand anatomical and effective connectivity of the epileptogenic networks. Previous work from our laboratory has demonstrated the usefulness of PGC to create dynamic directional temporal maps from multiple brain regions during spontaneous

seizures[11,3] and this thesis project derives from questions that emerged from earlier studies.

Epidemiology

Over 240 epilepsy syndromes have been described by the International League Against Epilepsy (ILAE), with idiopathic generalized epilepsy being the most common.[12] Seizures of temporal lobe ictal onset represent the most common type of localization-related epilepsy. Most outcome series report that temporal lobe epilepsy (TLE) account for 2% of the total group of epilepsy syndromes.[12] The incidence of TLE is estimated to be 30,000 cases per year worldwide.[13] The most common cause of TLE is hippocampus sclerosis (HS), a micro-structural developmental abnormality of the hippocampus characterized by cellular paucity and architectural disorganization. In addition to typical clinical findings, the diagnosis of HS is suspected with the identification of the following BMRI abnormalities: 1) focal atrophy, 2) changes in signal intensity, and, 3) reversal of the white-to-gray matter ratio.[14,15] The second most common type of localization-related seizures is extra-temporal lobe epilepsy, among which seizures of frontal lobe ictal onset is the most common.[16] Overall, patients with TLE and extra TLE typically developed partial complex seizures (PCS), a defining feature of partial epilepsy.

Significance and Rationale

Most cases of localization related epilepsy respond well to one or two AED. However, a small subset of patients with PCS and a focal IZ do not respond to conventional AED. This population is considered good candidates for epilepsy surgery if the IZ is well defined by ictal VEEG analysis, BMRI, interictal PET, ictal SPECT and Magnetoencephalography (MEG) techniques. Various areas of the temporal lobe have been identified in the genesis of epilepsy, specifically the mesial structures such as the

hippocampus formation and the para-hippocampal gyrus or medial structures such as the temporal cortex.[5] Although PCS usually emanates from mesial temporal lobe structures, it could also be originating from cortical temporal lobe areas or extra-temporal areas that are part of the limbic system (LS) such as the frontal lobe.[17] Evaluation of the limbic system is not usually possible in clinical practice, mainly because it involves intracranial electrophysiological recordings of its various components, i.e. mammillary bodies, anterior nucleus of the thalamus, cingulate gyrus, amygdala, orbital-frontal cortex, the entorhinal cortex and the hippocampus formation (Figure 2-1). Nevertheless, scientists in epileptology are interested in understanding the connectivity of the LS and its effects on function and behavior of the supportive neuronal circuits and defining mechanisms of seizure generation and propagation to more fully elucidate the epileptogenic network (EN).[18] Since seizures emanating from the mesio-limbic-temporal network (MLTN) are the most common type of PCS of temporal lobe ictal onset, studying animal models and patients with TLE will expand our understanding of the origin of this type of seizure. Study of PCS with an ictal onset on the MLTN can be achieved by a variety of non-invasive mechanisms such as VEEG, BMRI, SPECT, PET, MEG and effective connectivity measures. While seizure localization emanating from the LS structures using standard scalp interictal and ictal VEEG recordings is frequently challenging since the frontal and temporal lobes, morphological basis of the LS, share a common proximity not easily definable with non-invasive electrophysiological methods.[19] Furthermore, invasive procedures such as interictal and ictal subdural intracranial EEG recordings may sometimes show conflicting ictal onset data. Overall, the quandary for specific ictal onset localization is to determine

whether a specific neural network is responsible for seizure generation and if interventions within this network can modify the mechanism and eventually improve seizure control.[3]

Biology of the Neuronal Circuitry

Myelination is a complex and well-organized process that begins early in embryonic life and does not end until adulthood.[20, 21,22] When a neuron is excited by stimuli, the electrical impulse flows down the length of the axon following the path of lower resistance, i.e. through the Ranvier nodes, avoiding the high resistance surface of the myelin sheet. The electrical impulse then opens the voltage dependent calcium channels, causing an influx of calcium, leading to the fusion of the synaptic vesicles and release of neurotransmitter (NT). Then, sodium flow increases and potassium flow decreases, leading to the generation of an action potential. This complex group of changes leads to depolarization of the axon at the next axonal node. The process rapidly propagates due to the low capacitance of the myelin sheet and high conductivity properties of the Ranvier nodes. This entire mechanism is modulated by NTs, of which the most important is the gamma-amino-butyric acid (GABA).[23] Due of its inhibitory properties, a GABA deficient state promotes an epileptogenic environment.[24, 25, 26]

Non-Lesional Epilepsy

Non-lesional pharmaco-resistant partial epilepsy (NLPE) refers to the presence of PCS documented by ictal EEG recording, normal conventional BMRI studies and lack of therapeutic response to at least two AED for at least one year. Modern imaging and electrophysiological technologies have been developed with the aim of better understanding abnormalities within the neural networks.[27] These developments lead to a very practical question: How can we define structural connectivity of the neuronal

circuitry and as a consequence the IZ? From a practical standpoint, most clinical epileptologists attempt to answer that question by admitting the patients to an epilepsy center to conduct a phase one and a phase two evaluation. During phase one, the patients are admitted to the Epilepsy Monitoring Unit (EMU) to undergo a continuous VEEG telemetry study over five to seven days. The VEEG is performed with the aim of capturing several seizures and determine seizure semiology and the IZ based on scalp EEG analysis. Additional tests are also performed, depending on the situation of each case which may include non–contrast BMRI, neuropsychology testing, SPECT, PET, MEG and the intra-carotid sodium amobarbital procedure (ISAP), also known as the Wada test, in honor of the Canadian neurologist Juhn Wada. [28] [29] After completion of phase one, the phase two evaluation consists of implanting subdural electrodes and grids in the areas suspicious to be the IZ. The patient is observed for seven to ten days with the aim of capturing more typical unprovoked PCS to further delineate the IZ by invasive electrical recordings. Also, a functional mapping of the brain is performed using a GrassS12 isolated biphasic cortical stimulator (West Warwick, RI) in cases where the IZ is close to or within cortical eloquent areas such as the motor strip, Broca's area or Wernicke's areas. The mapping is done to define the narrowest or smallest region to avoid damage to critical areas at the time of surgery, to prevent further damage of these critical zones. Once identified, a limited surgical resection of the IZ would be expected to improve quality of life, making the patient seizure-free and causing minimal or no postsurgical deficits. Ideally, NLPE patients that endure such as extensive work up should become seizure- free (Engel classification 1A) or making a significant improvement in seizure control (Engel classification 1B).[30] However, even with all the

aforementioned invasive and non-invasive procedures aimed to define the IZ leading to an appropriate surgical resection, seizure outcomes continue to lag behind patients' and the general public expectations as reported by many series worldwide.[31, 32] Accordingly, further development of non-invasive and invasive tools that allow precise dissection of the IZ will lead to proper understanding of the neural connections within and outside the IZ and subsequent translation to improved surgical resections and long term outcome.

Based on prior research experience,[8,33] we believe that using an effective connective measure such as PGC in the animal model of spontaneous seizures and in patients with NLPE would allow us to define maps of neuronal circuitry heavily involved during ictal generation and propagation.[34] In order to define such neuronal circuitry, it is imperative to establish directionality at time of ictal onset. Thus, we hypothesized that seizure directionality can be predicted by using PGC analysis of ictal EEG recordings. The null hypothesis is that the IZ in patients with PERT originate in a single neuronal network and propagates to the contra-lateral hemisphere (inter-hemispheric ictal propagation). The alternative hypothesis is that the IZ originate in one hemisphere and do not propagate to the contra-lateral hemisphere. We designed a case control study to define linear PGC measures in subjects with PCS of mesio-limbic temporal network IO and using a case series study. This research work is an analysis on defining the directionality of seizure propagation in our studied population and is part of a prospective longitudinal study in children and adults with a diagnosis of NLPE.

Is the EEG the Right Tool to Evaluate Ictal Networks?

Growing evidence, in both animal models and in human studies, indicates that specific neural networks are responsible for the ictogenicity of the brain.[1] Specific data demonstrates that cortical and subcortical networks are primarily responsible for seizure

generation in both partial and generalized epilepsies.[35] A number of authors have defined the neural networks in different ways.[36,37] However, most neuroscientists define neural network as a group of functionally and/or anatomically related structures, with unilateral or bilateral representation with the particular feature that activity in one area may affect the entire network.[2,38] Supportive evidence is based on clinical information obtained from patients with PCS, ictal and interictal VEEG findings, functional information from SPECT and PET, intracranial electrographic subdural monitoring and long term surgical outcome studies.[39 40] There is excellent scientific evidence of at least three main neural networks: the MLTN, parietal/ frontal, and posterior/occipital.[6] Additionally, there is evidence suggestive of at least two other, less well defined networks: bilateral frontal and parietal/temporal networks.[38]

The MLTN is conformed by the following anatomic structures: 1) hippocampi, 2) entorhinal cortices, 3) amygdala, 4) lateral temporal neocortices, 5) various extra-temporal structures of the frontal lobe and 6) the medial thalamus. Figure 1-1 depicts the hippocampus and its connectivity as it was described by Cajal in 1911. Dysfunction of part or the whole network is the basis for the clinical and electrographic manifestations of seizure activity. In this case, it becomes irrelevant to point to the specific ictal onset zone because the entire network is affected as a whole. Also, seizures may propagate in various directions involving other regions of the brain away from the primary neural network. The actual IZ may vary within the same subject and even may be different during each seizure, because the seizure onset may occur in any part of the network. This network variability has been demonstrated several times with intracranial electrode recordings.[41] In theory, interruption of the epileptogenic network

may cause seizure expression to stop or at least to be modified. The stereotypical features of clinical seizures can be demonstrative of this network variability. [42] Also, seizure variability may be due to propagation of the electrical activity to other non-related areas of the brain. This concept has been proven in patients with occipital epilepsy during which seizures usually propagates to the anterior temporal lobes. Clinically, the patient may have frontal lobe symptoms although the frontal lobe is not part of the occipital network.

PET scans have been of value when evaluating patients with temporal lobe epilepsy. This tool provides interictal information of the brain activity and the specific network of interest. The main function of PET is to demonstrate hypo-metabolism in the areas of the neural network in question. This hypo-metabolic process is documented by areas that light up after a radiotracer, typically radio-labeled glucose, is injected intravenously into a patient. There is extensive evidence that PET scans show areas of hypo-metabolism in the medial temporal cortex, lateral temporal cortex, thalamus, amygdale and inferior frontal lobe areas in subjects with seizures originating from the MLTN.[43,44] Surgical excision of the anterior temporal pole demonstrates changes in the number of seizures emanating over the temporal/limbic networks.[45] PET typically reveals improved metabolism of the adjacent regions that are part of the MLTN such as the frontal regions ipsilaterally to the brain areas that has been excised.[46] The excellent response to a surgical intervention is also used as evidence to support a neural network as the cause of focal seizures. Performance of an anterior temporal lobectomy procedure with the aim of controlling seizures in patients with MLTN epilepsy has shown a significant modification of the number and duration of the events, which may remain

absent for years in some cases.[38] At the cellular level, multi-channel recordings of the CA1 region and dentate gyrus of the temporal lobe, have been used to define the concept of neural networks.[3] Finally, neuro-physiologic studies report a consistent spatial, temporal and hierarchical relationship regarding the initiation, propagation and termination of seizures in rats where the seizure spreads from the CA1 region to the ipsilateral dentate gyrus and the contra-lateral hippocampus.[11]

Effective and Functional Connectivity Tools in Epilepsy

To better understand the connections between the different neural networks, additional tools have been developed to look at the anatomic and functional connectivity of the brain.[47] Two categories of tools are available to study this type of connectivity and its effects: functional and effective. Overall, both types of connectivity measurements evaluate the relationships between brain regions based on analysis of time series obtained from ictal and interictal electrographic recordings and may lead to the ability to predict and measure seizure directionality. Functional connectivity measures, (direct transfer, cross correlation and coherence), demonstrate patterns of statistical dependence. Effective connectivity (partial direct coherence and PGC), analyzes causal influences of one neuron over another.[3] Coherence, a functional connectivity measure that determines frequency power changes occurring in a system, has demonstrated a modest improvement in our understanding of brain connectivity in part for its lack of meaningful causal relationship and directionality information.[7] In contrast, PGC have consistently shown a positive directionality and co-registration. PGC is a statistical method that attempts to relate interactions of neuronal circuitry based on a linear regression model between two time series. The general theory of PGC dates back to the 1950's and 1960's from the theory of prediction in the field of economics when

Wiener proposed that for a two simultaneously measured time series, one series can be considered causal of the second if is possible to predict the second series by incorporating elements of the first.[48] The way that we understand Granger theory today is based on the fact that if the variance of the predictive error of one time series is diminished by incorporating values of the second time series using a regression model analysis, then the first time series have a directional (causal) influence on the second series.[49]

Currently, PGC is used as a predictive technique in various areas of the neuroscience fields including evaluation of extracellular potential fields[50], responses from antero-ventral cochlear nucleus neurons[51] as well as non-neurosciences fields such as estimation of Brownian simulations and unidirectional influx diffusion fields[52] and predictions of optical properties in nanocomposites for nanomedicine.[53] In a simple model of two neuron network, in which neuron one is directly connected to neuron two, PGC causality can easily define direct causal correlation and discriminate its directionality.[54] However, there are more complex limitations in large neuronal networks where several influences are exerted among the neurons of the network. Consider the case of three neurons network, in which one is connected to two and two is connected to three but without any direct physical connection between one and three. PGC analysis will correctly determine causal relationship between neuron one and neuron two and between neuron two and neuron three. However, PGC can also erroneously determine a causal relationship between neuron one and three although no physical connection is established between neuron one and three, if the activity of neuron one affects neuron three, but only through the effect of neuron two. Also, neuron two may

exert an effect on neuron three and if such effect is distorted by neuron one, it would not any longer represent a true reflection of the effect of each element on the other. Thus, the causal relation of two neurons can be affected by the effects of a third neuron that is not measured and Granger causality will indicate a causal relationship that does not exist. This is the so-called “hidden unit effect” which affects most statistical processes.[8] Time scale and sampling rates are also two very important variables that can have antagonist effects in the analysis of the PGC method but that should be carefully considered in anticipation of any PGC analysis.

Our capability to localize IO and better define the IN is a very important step for the successful planning of surgical resection of epileptogenic foci for seizure control in patients with pharmaco-resistant epilepsy. Most seizures can be fairly well identified, lateralized and localized with combination of EEG recordings, seizure semiology analysis and advanced brain imaging modalities. However, some seizures are not able to be localized even with the use of intracranial electrode recordings. Possible explanations include: 1) fast intra-ictal activation and spread, or 2) fast regional spread and a limited visual analysis that do not yield localization information. Clearly, additional methods of visualization would be helpful for better seizure localization. Various methods have been applied to ictal EEG analysis but most of them use spike and seizure detection rather than localization.[55] Several authors have made outstanding contributions using seizure localization methods when evaluating epochs from subdural electrodes and intracranial scalp EEG data with the ultimate goal of determining ictal onset, propagation and directionality.[5,10] The advantage of seizure localization methods such as autoregressive models is that allows drawing patterns of flow of activity that

lead to the creation of maps of neuronal circuits. With the advent of appropriate software programs and improved computational ability, the autoregressive methods, such as PGC have become extremely popular to help understand seizure localization and propagation. Power spectra, coherence and phase spectra have been used in the past. Multiple other methods have been developed including multilag cross-covariance functions, coherence/phase analysis, and coherence comparison. However, such methods do not provide information of flow of activity.[56] Even direct coherence methods based on an autoregressive models are limited to analysis between two channels. Other methodologies available such as the direct transfer function developed in 1991 by Kaminski and Blinowska is a multichannel autoregressive model in which patterns of flow of electrical activity can be determined.[13] Franaszczuk, et al. in 1994 validated and implemented the method in a sample of subjects with intracranial recordings.[57] One common ground with the various described methodologies is that they analyze linear and non-linear brain activity. Patterns of brain activity are frequently non-linear, and it is not fully established whether linear or non-linear methods are best for seizure analysis. Non-linear methods can be used to analyze the brain activity even if much of such data is non-linear (chaotic). In contrast to what is seen in clinical practice with the use of MEG, interictal spikes are likely not a good source of linear analysis for use with non-linear methods. When adjacent channels are not highly correlated, then non-linear methods are recommended. And the opposite is also true: linear analysis can be applied when high correlation exists between adjacent channels.[58] For all these reasons, there is still a clear limitation of the PGC method, of which the main weakness is that does not provide information on the mechanisms of seizure generation. Certainly,

the situation becomes more complex and relevant when several neurons of a particular network are involved, which is what neuroscientists and clinical neurophysiologists see in real life. Then, our laboratory is interested in understanding how PGC define directionality measures in humans with PCS of mesio-limbic temporal network ictal onset. Thus, we hypothesized that ictal directionality between two selected brain regions of the same neuronal networks in subjects with epilepsy refractory to medical treatment can be predicted in humans with the use of the effective connective auto-regressive model linear PGC, a finding not yet reported in the medical literature.

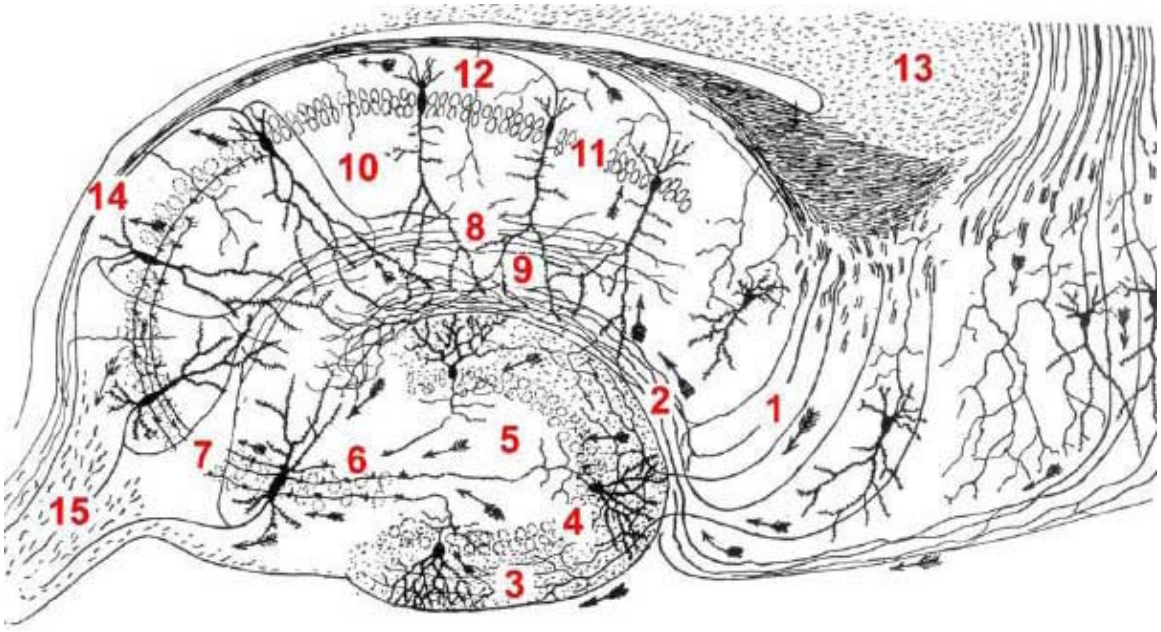

Figure 1-1. Hippocampal anatomy and connectivity as depicted by Cajal in 1911.1 = subiculum, 2 = perforant pathway axons, 3 =molecular layer, 4 = granule cell layer, 5 = hilum, 6 = mossy fiber axons, 7 = CA3 pyramidal neurons, 8 = Schaffer collateral axons, 9 = stratum lacunosum moleculare, 10 = stratum radiatum, 11 =CA1 pyramidal neurons, 12 = stratum oriens, 13 = dorsal hippocampal commissure, 14 = alveus, 15 =Fimbria. (Source: S. Cajal, Histologie Du Systeme Nerveux De LHomme Et Des Vertebretes A. Maloine,Paris, 1911).

CHAPTER 2
METHODS

General Methods

We conducted a prospective longitudinal study in children and adults with a diagnosis of partial epilepsy intractable to medical treatment. Patients were included if they had a history of unprovoked PCS who had failed two or more AED for at least one year. The patients underwent a continuous five to seven days VEEG and a 3.0T BMRI during an admission to the Epilepsy Monitoring Unit at Shands Hospital at the University of Florida. The subjects were recruited from the population followed through the pediatric and adult comprehensive epilepsy programs in the departments of pediatrics and Neurology respectively using the inclusionary and exclusionary criteria set forth below.

At entry, the following inclusion criteria had to be met: (1) patients with a diagnosis of medically intractable partial epilepsy according to the ILAE diagnostic criteria; (2) ages between 6 months and 70 years at time of enrollment. Patients were excluded when they had: 1) progressive neurodegenerative disorder, 2) unwilling to participate in the study, 3) less than 6 months of age, and/or 4) history of brain tumor or traumatic brain injury.

This research work, involving human subjects, was approved by the University of Florida Institutional Review Board (IRB) and patients were enrolled from September 1, 2009 through January 31, 2011. All participants provided written, informed consent. All minors provided informed assent and written consent was obtained from the parent or guardian after a complete description of the protocol and answers to any given

questions. The patients will be followed prospectively for two years after surgery to determine outcome using Engel's classification[30].

Specific Methodology for PGC Analysis

A total of ninety partial complex seizures were analyzed in twenty-three subjects with epilepsy refractory to medical treatment. Current standards of care entail extensive observation and analysis of ictal EEG data by trained neurophysiologist and EMU staff. Thus, the aim of the study was to use PGC on prospective ictal EEG recordings to provide directional functional maps of the brain regions associated with the IN. Data for seizure analysis were collected using a standard 21 channel VEEG recording system, the Nicolet NicVue-Viasis (San Diego, CA). Settings were consistently used in all ictal events and stored with the video recording for each patient. Then, the events were cut in a way that only included VEEG data of five minutes before ictal onset, ictal epochs and five minutes of post-ictal EEG activity. All protected health information was removed; the video component and only the interictal and ictal EEG raw data was used for analysis. Multichannel PGC analysis of the EEG recordings was performed using the toolbox developed by Seth in 2010.[59] Seth's toolbox was developed as an exploratory mechanism for general purpose of PGC analysis, which can be utilized and deployed with minimal training by any reasonable Matlab (Natick, MA) enthusiast.

The toolbox implements a statistical interpretation of causality in which neuron one influences the activity on neuron two, if knowing the past of neuron one can help predicting activity of neuron two, better than just knowing the past of neuron two alone. Thus, the toolbox utilizes an autoregressive model in which a sample of time series is analyzed as a weight sum of past values. This toolbox presents several linear models of continuous time series. First, the toolbox subtracts the best fitting line (detrending) and

removes the mean from each time series (demeaning).Then, the toolbox checks that all variables are covariance stationary using various statistical tools. A key parameter choice for PGC analysis is determining the model order, i.e., the number of previous observations, to account for an appropriate estimation of the auto-regressive model. Thus, is important to avoid selecting model order that is too low because the regression model will not capture dynamic relations of the analyzed data. Although there are several methods to establish the model order, we elected to automatically select the model order according to the Bayesian information criterion (BIC) [60] and the Akaike information criterion.[61] Then, we decided to select a model order of 200, as a conservative estimate. The next step was to determine the best way to compute PGC in a fully conditional manner. As no consensus exists as to the most appropriate analysis, we used bootstrapping rather than any of the other established methods (such as shuffling and surrogate analysis). We decided to perform computational intensive bootstrapping as a mean of addressing the issue of statistical significance of the PGC in the EEG samples analyzed. This test allowed checking significance of the quantities calculated by the functions of the toolbox that have distributions that are analytically known. Bootstrapping is a useful tool to establish confidence intervals around a value which can be used to distinguish them from zero or to compare with other values. Following the same conservative thought process, we decided to do 1,000 bootstraps resampling for a more rigorous test. The duration of the approximate interval for PGC analysis was determined by visual examination of the EEG records. Then, PGC in the frequency domain was computed. The data were plotted for each pair of electrodes analyzed (Table 2-1). All the analyses were performed for research purposes and at no

time were the analyses used for clinical management or medical decision making. The EEG recordings were scrutinized for seizures using automated detection algorithms and by verification performed by an expert adult epileptologist and a pediatric epileptologist as part of the standard of care offered to our patients admitted for presurgical evaluation to the EMU. The first part of the study consisted on testing seizure directionality in subjects with PCS of MLTN ictal onset. Thus, to test the null hypothesis, we evaluated directionality by performing PGC on seizures with an ictal onset over the left frontal area (electrode F7) propagating contra-laterally towards the right temporal region (electrode T8, inter-hemispheric hypothesis). Figure 2-1 shows the specific location of each electrode. As a control, PGC was calculated for the same electrode involved in seizures with an IO over the left frontal region (F7) and compared with the left temporal region (electrode T7). This procedure was performed for the same seizure on each subject. Thus, PGC analysis was obtained in a sample of nineteen ictal events with an IO over the let frontal region, as determined by a visual analysis of VEEG recordings by trained clinical neurophysiologists unrelated to the study. PGC values are included in Table 3-2. Then, we tested the significance of the intra-hemispheric seizure propagation and compared such output against the inter-hemispheric data. Hence, we tested the directionality of seizures with an IO over the left temporal region (T7) and propagating intra-hemispherically towards the left frontal region (F7) and calculated PGC in a sample of twenty-eight seizures with the IO over the left temporal network. As a control, PGC was calculated on ictal EEG raw data of seizures with an IO over the right temporal region (T8) and propagating towards the right frontal regions (F8). It is important to clarify that electrode T7 (left temporal) and electrode F7 (left frontal)

evaluate the left hemisphere, whereas, electrode T8 (right temporal) and electrode F8 (right frontal) evaluate the right hemisphere. Both sets of electrodes (T7-F7 and T8-F8) are placed across hemispheres, which will allow us testing whether it was ipsilateral or contra-lateral propagation. This procedure was performed for the same seizure on each subject to test whether there was inter-hemispheric or intra-hemispheric seizure propagation. Furthermore, we decided to evaluate inter-hemispheric seizure directionality but using a different brain region in order to confirm our findings using similar electrode but two different brain networks. The aim was to test a neuronal network different than the temporal network and compare such data with a different network located within the same hemisphere. Thus, we tested the directionality of seizures with an IO over the right frontal area (electrode F8) propagating ipsilaterally towards the right temporal region (electrode T8, intra-hemispheric hypothesis). The aim of this part of the study was to confirm previous PGC findings on inter-hemispheric propagation. As a control, PGC was calculated for the same electrode involved in seizures with an IO over the right frontal region (electrode F8) but compared with the left frontal region (electrode F7) which is located across hemispheres. This procedure was performed for the same seizure on each subject. Accordingly, PGC analysis was obtained in a sample of 26 seizures with an IO over the right frontal region, as determined by a visual analysis of VEEG recordings by a trained independent clinical neurophysiologists not involved with the research study.

Finally, we retested our results comparing seizures with a focal IZ against another unrelated area of the brain, not believed to be part of the MLTN. Consequently, we tested directionality of seizures with an IO over the right temporal area (T8) propagating

ipsilaterally towards the right frontal region (F8, intra-hemispheric hypothesis). As a control, we selected raw data from the right parietal network (electrode P8) and compared with the left central region (electrode C3) which is located across hemispheres. This procedure was performed for the same seizure on each subject. As a consequence, PGC analysis was obtained in a sample of sixteen unrelated seizures with an ictal onset over the right temporal region, as determined by a visual analysis of VEEG recordings. Figure 2-1 summarizes the interventions performed during phase 1.

The second part of this study was designed to evaluate if there was statistically significant inter-hemispheric propagation using as a control a network not related to the MLTN. This part of the study consisted in comparing directionality measures obtained with PGC on the electrodes that oversee the frontal and temporal areas and compare with electrodes that look at a different network; in this case we choose the electrodes that record electrical activity from the parietal network as a control. Hence, we followed a similar procedure as it was performed for the first part of the study (Table2-2). First, we evaluated directionality by performing PGC on seizures with an IO over the left frontal area (electrode F7) propagating contra-laterally towards the right temporal region (electrode T8). As a control, PGC was calculated for the electrode that oversees the left central region (C3) and compared with the right parietal region (electrode P8) which is located across hemispheres. Thus, PGC analysis was obtained in a sample of nineteen ictal events with an IO over the let frontal region (electrode F7), as determined by a visual analysis of VEEG recordings. Then, we tested the significance of the seizure directionality of twenty-seven ictal events with IO over the left temporal region (T7) and propagating towards the right frontal region (F8) and use as controls electrodes C3-P8.

Furthermore, we evaluated seizure directionality of twenty-six events with an IO over the right frontal area (electrode F8) propagating contra-laterally towards the left temporal region (electrode T7). As a control, PGC was calculated for the electrodes that look at the right central region (C4) and propagates towards the left parietal region (P7). Finally, we tested directionality of sixteen seizures with an IO over the right temporal area (electrodeT8) propagating towards the left frontal region (electrode F7) and used electrodes C4 and P7 as controls.

Statistical Methods

Most formulas for sample size calculation are dependent on the standard deviation (SD). However, that information was not available and there were no prior studies using the functional connectivity tool PGC to extrapolate that information as a comparison for our study. Therefore, we used the concept of empirical rule[62] to estimate that 95% of observations falls between the mean at +/- 2 SD. We were willing to commit a maximum acceptable error of 5% of the standard deviation at a 95% level of confidence. Hence, the error was estimated to be SD/10. Then, we determine the sample size using the formula of N=square of dividing Z-score by the error.[63] Then, the formula becomes N= (1.96X5) (1.96x5), which equals 96 as our sample size. In order to increase the power of the statistical test, we increase the sample size to 125 and elected a parametric test as statistical procedure. We did not use the more widely acceptable t–test because more than two different samples were compared. We elected one way ANOVA for two reasons: 1) it is recommended for use when the researcher is using two or more samples, and 2) ANOVA is statistically equivalent to other more widely accepted experimental analysis such as t-Student when testing more than two independent samples. We define a statistically significant finding as a p-value ≤ 0.05.

We encountered several problems with reaching the sample size target 1) EEG recordings did not fulfill the AIC/BIC requirement, 2) EEG recordings not able to be used due to technical reasons, and 3) some of the events captured were not considered by independent neurophysiologist actual epileptic seizures. Therefore, we only analyzed ninety seizures instead of the originally aimed sample of one hundred and twenty five seizures. P values were calculated following one way ANOVA as statistical procedure and using the data obtained with linear PGC.

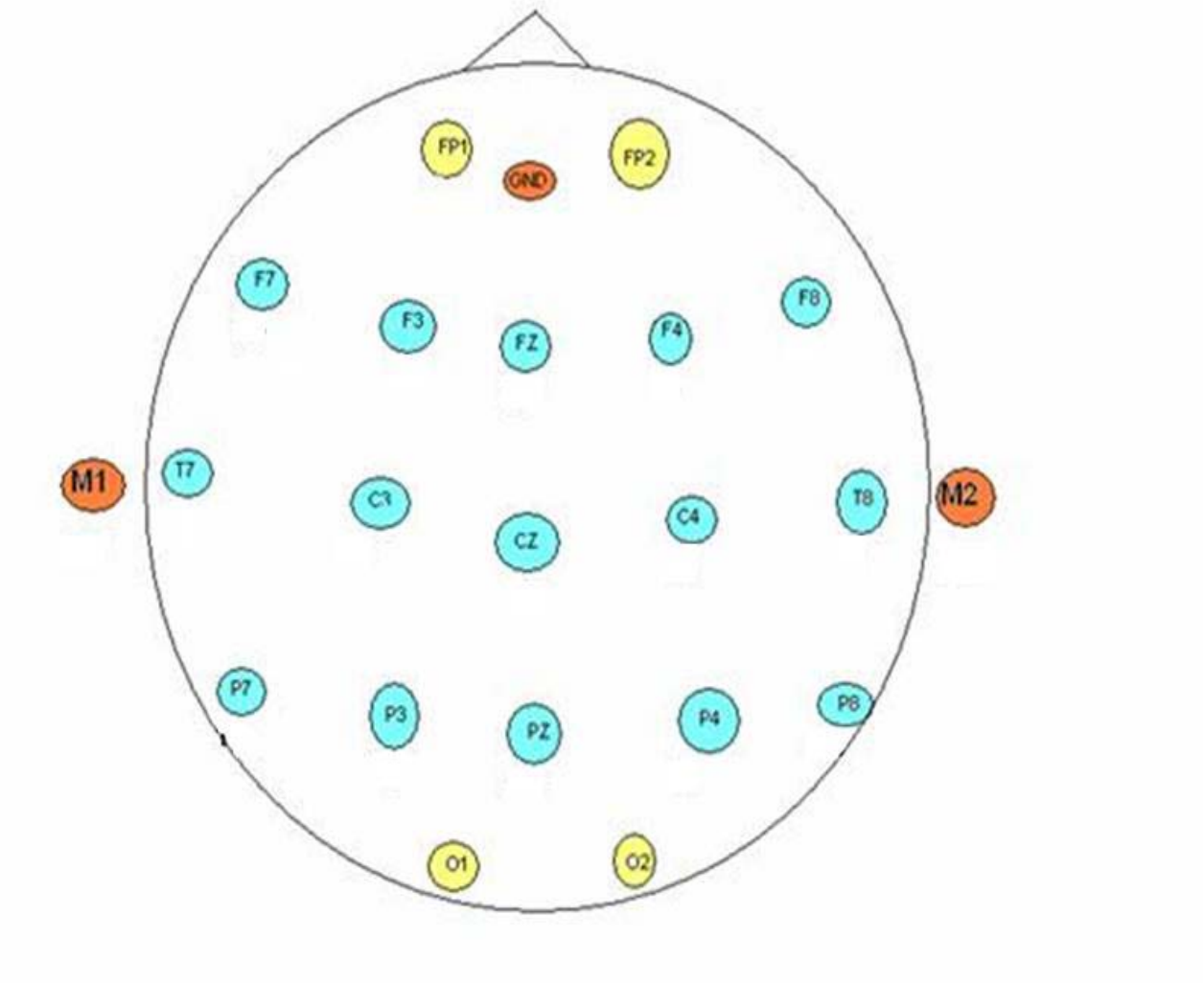

Figure 2-1. Electrode placement localization. The figure depicts electrode placement localization using the international 10:20 electrode placement and a double banana montage on a conventional routine EEG. F7: left frontal, T7: left temporal, F8: right frontal, T8: right temporal (Source http://www.picobay.com/projects/. Last accessed February 18, 2011)

Table 2-1. Phase 1 list of montages use to test inter-hemispheric and intra-hemispheric hypothesis using linear PGC methodology.

Formulation	Cases	Controls
Left Frontal(F7)	F7-T8	F7-T7
Left Temporal(T7)	T7-F7	T8-F8
Right Frontal(F8)	F8-T8	F8-F7
Right Temporal(T8)	T8-F8	P8-C3

Table 2-2. Phase 2 lists of montages used to test the inter-hemispheric hypothesis using linear PGC methodology.

Formulation	Cases	Controls
Left Frontal(F7)	F7-T8	C3-P8
Left Temporal(T7)	T7-F8	C3-P8
Right Frontal(F8)	F8-T7	C4-P7
Right Temporal(T8)	T8-F7	C4P7

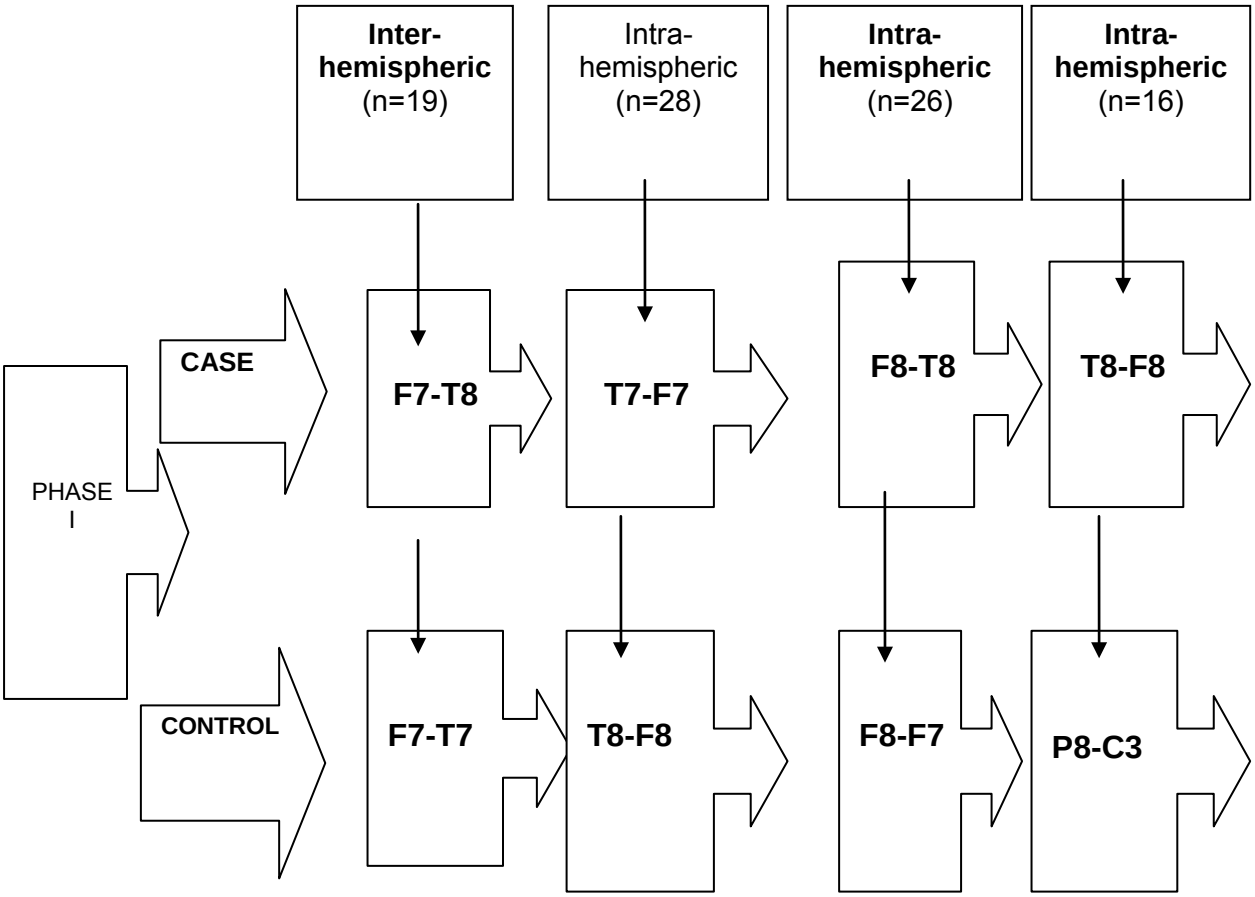

Figure 2-2. Study phase 1 methodology.

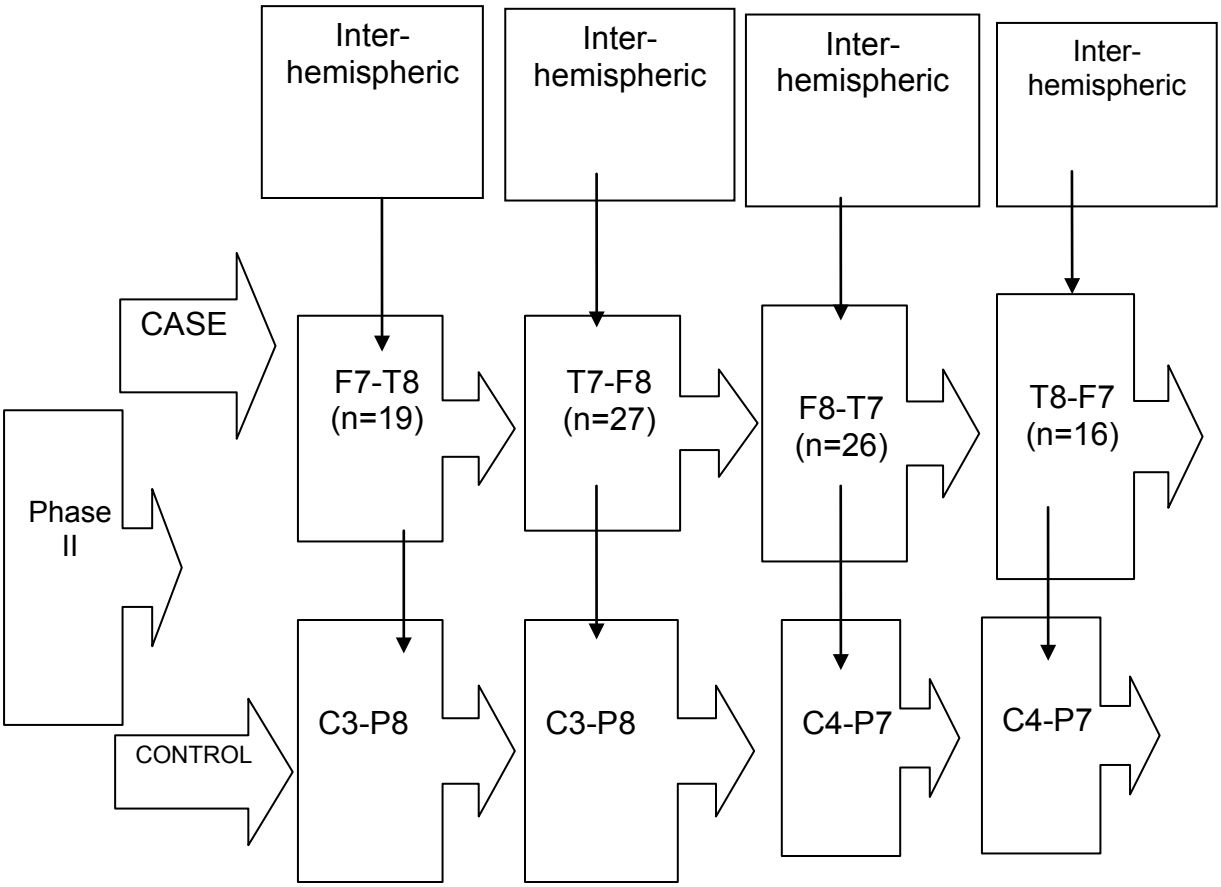

Figure 2-3. Study phase 2 methodology.

CHAPTER 3
RESULTS

We prospectively enrolled twenty-three patients with partial epilepsy refractory to medical treatment for a continuous five day VEEG study evaluation and PGC analysis and identified ninety seizures suitable for analysis. The cohort under study consisted of ten female and fourteen male patients with ages ranging between fourteen months and fifty-eight years of age. The overall descriptors were: age at entry in years (or a fraction), gender, number of PCS analyzed per subject, number of previously failed AED, age of onset of epilepsy and localization of ictal onset based on EEG studies. Table 3-1 summarizes the diagnostic and clinical characteristics of the patients at the time of entry. Table 3-2 summarizes the actual PGC values that lead to our conclusions. Inter-hemispheric propagation for seizures with an IO on the left frontal region (F7-T8) was demonstrated by the fact that directionality was statistically significant (p 0.0028) when compared against controls (F7-T7). Figure 3-1 demonstrates seizure directionality of events originating over the left frontal region and extending towards the right temporal region and compared using data emanating from the same left frontal lobe and extending ipsilaterally (left temporal lobe). Therefore, this is demonstrative of inter-hemispheric extension of ictal events with a mesio-limbic temporal network ictal onset. Subsequently, intra-hemispheric seizure propagation was identified for seizures with IO over the left temporal region (T7-F7) based on the fact that directionality was significant (p 0.0548) when compared against controls (T8-F8).This is demonstrated on Figure 3-2, depicting statistically significant seizure directionality of events with onset over the left temporal lobe propagating ipsi-laterally (red line) ,and, compared using as controls electrodes that over see the right temporal

lobe (green line) with ipsilateral propagation(T8-F8). Such finding is indicative of intra-hemispheric propagation. Furthermore, intra-hemispheric propagation for seizures with an IO on the right frontal region (F8-T8) was demonstrated by the fact that directionality was statistically significant (p 0.0558) when compared against controls (F8-F7). Figure 3-3 is a scatter plot of all PGC values for both cases and controls and shows that these values were significantly higher in the group of seizures with an ictal onset over the right frontal region (red line) with ipsilateral propagation (electrode F8) than the ictal events with onset over the same electrode (F8) with contra-lateral left frontal propagation (green line). Thus, this is proof of intra-hemispheric propagation. Last, intra-hemispheric extension for seizures with an IO on the right temporal region (T8-F8) was proven due to the fact that directionality was significant (p 0.0257) when compared against controls (P8-C3). This is depicted on Figure 3-4 which illustrates that seizure directionality was consistently higher in cases (red line) when compared against controls (green line). Hence, intra-hemispheric propagation was established. The fact that inter-hemispheric directionality and not intra-hemispheric was identified in subjects with PCS of MLTN, led us to design a second part of this study to evaluate this finding. Consequently, the second part of our work consisted in comparing PGC on the electrodes that over see the frontal and temporal areas, morphological basis of the MLTN and compares such data against the electrodes that look at a different network, like the parietal network as a control. There were no statistically significant differences for the inter-hemispheric PGC measures for seizures with an IO on the left frontal (p=0.2882).and no significant directionality for ictal events over the left frontal region as compared against left parietal network (Figure 3-5). Similarly, no significant difference was identified on events with

ictal onset over the left temporal (p=0.1572). There were also no significant differences on ictal directionality between cases (left temporal) and controls (left central) (Figure 3-6). No statistically significant directionality was identified on seizure with onset over the right frontal (p=0.6772) (Figure 3-7). Finally, no directionality was identified on seizures with ictal onset over the right temporal regions (p=0.7795). Figure 3-8 illustrates that there was no significant directionality found when compared seizures emanating from the right temporal lobe network and the right parietal network. Figure 3-9 illustrates the average and standard deviation of the PGC measurements of the group of seizures with a MLTN ictal onset. The PGC findings are shown in Table 3-3. To summarize, using the effective connectivity measurement PGC we have demonstrated that it is possible to predict intra-hemispheric or inter-hemispheric seizure propagation based on accurate defining directionality on analysis of ictal EEG raw data.

Table 3-1. Patient diagnoses and demographics

Patient	Gender	Age	PCS (number)	Total AED	Age onset (years)	Localization
1	F	12	4	5	0.1	Temporal
2	F	23	6	3	13	Frontal
3	M	51	4	5	1	Temporal
4	F	3	5	6	0.5	Front-Temp
5	M	17	5	8	8	Front-Temp
6	M	11	5	3	9	Front-Temp
7	M	6	5	5	0.6	Frontal
8	M	11	5	2	0.5	Frontal
9	F	57	5	11	5	Front-Temp
10	M	4	3	2	1	Temporal
11	F	14	5	10	2.5	Frontal
12	F	2	3	2	0.5	Frontal
13	M	1.5	1	2	0.5	Temporal
14	F	20	5	6	16	Front-Temp
15	M	51	1	9	12	Temporal
16	M	13	3	3	7	Front-Temp
17	M	6	1	3	2	Frontal
18	F	13	5	5	1	Front-Temp
19	F	20	7	2	16	Temporal
20	F	24	2	4	16	Temporal
21	F	10	1	2	3	Temporal
22	M	22	5	5	11	Frontal
23	M	10	4	2	8	Temporal

Table 3-2. Inter and Intra-hemispheric PGC values for subjects with PCS of MLTN ictal onset

Region	Left frontal	Left temporal		Right frontal			Right temporal	
	Case	Control	Case	Control	Case	Control	Case	Control
Seizure	F7-T8	F7-T7	T7-F7	T8-F8	F8-T8	F8F7	T8-F8	P8-C3
1	6	1	0	2	0	4	2	3
2	5	0	2	1	4	4	8	5
3	4	6	1	3	6	3	4	0
4	2	2	1	3	8	2	1	2
5	7	2	6	2	7	1	1	2
6	3	2	4	2	3	4	5	2
7	3	4	2	1	3	0	6	3
8	3	1	2	2	2	1	3	1
9	8	3	3	2	1	0	5	4
10	4	2	2	4	7	0	6	2
11	4	2	4	4	5	2	1	2
12	3	3	3	4	6	4	4	2
13	5	3	3	1	4	6	6	3
14	1	2	4	4	4	2	5	1
15	5	1	5	2	0	6	1	3
16	5	2	5	3	4	2	2	1
17	3	3	7	1	5	6		
18	2	2	5	6	1	1		
19	3	4	7	2	5	3		
20			6	4	2	1		
21			9	1	2	1		
22			0	3	4	4		
23			5	4	3	3		
24			2	3	4	3		
25			2	1	3	0		
26			5	5	0	1		
27			1	3				
28			7	2				
Average	4	2.3684	3.6786	2.6786	3.5769	2.4615	3.75	2.25
SD	1.7638	1.3421	2.3421	1.3348	2.2122	1.8811	2.2361	1.2383
P-value	0.0028		0.0548		0.0558		0.0257	
Sample	19	19	28	28	26	26	16	16

Table 3-3. Inter-hemispheric PGC values for subjects with PCS of MLTN ictal onset using the parietal network as a control

Region	Left Frontal		Left Temporal		Right Frontal		Right Temporal	
	Case	Control	Case	Control	Case	Control	Case	Control
Seizure	F7-T8	C3-P8	T7-F8	C3-P8	F8-T7	C4-P7	T8-F7	C4-P7
1	6	3	3	2	3	0	3	3
2	5	3	4	1	3	2	0	3
3	4	4	3	5	3	12	2	2
4	2	1	2	2	7	6	5	4
5	7	3	1	2	3	1	7	4
6	3	2	3	1	4	7	5	2
7	3	3	1	4	3	5	0	1
8	3	5	8	4	7	2	2	5
9	8	3	2	3	5	1	2	2
10	4	6	7	4	2	4	2	4
11	4	3	3	1	5	4	5	2
12	3	3	9	2	2	2	2	3
13	5	5	2	2	1	4	7	3
14	1	0	5	5	6	4	4	3
15	5	4	2	6	3	10	2	3
16	5	5	7	2	6	1	1	6
17	3	5	2	3	12	1	2	1
18	2	2	3	1	3	2	5	2
19	3	5	6	3	1	3		
20			9	5	3	2		
21			5	5	3	2		
22			3	3	7	3		
23			2	1	4	5		
24			3	4	3	5		
25			2	2	1	6		
26			2	3	3	1		
27			2	4				
Ave	4	3.4211	3.7407	2.963	3.9615	3.6538	3.1111	2.9444
SD	1.7638	1.539	2.3954	1.4802	2.4246	2.8558	2.139	1.3048
P-Val	0.2882		0.1572		0.6772		0.7795	
Sample	19	19	27	27	26	26	18	18

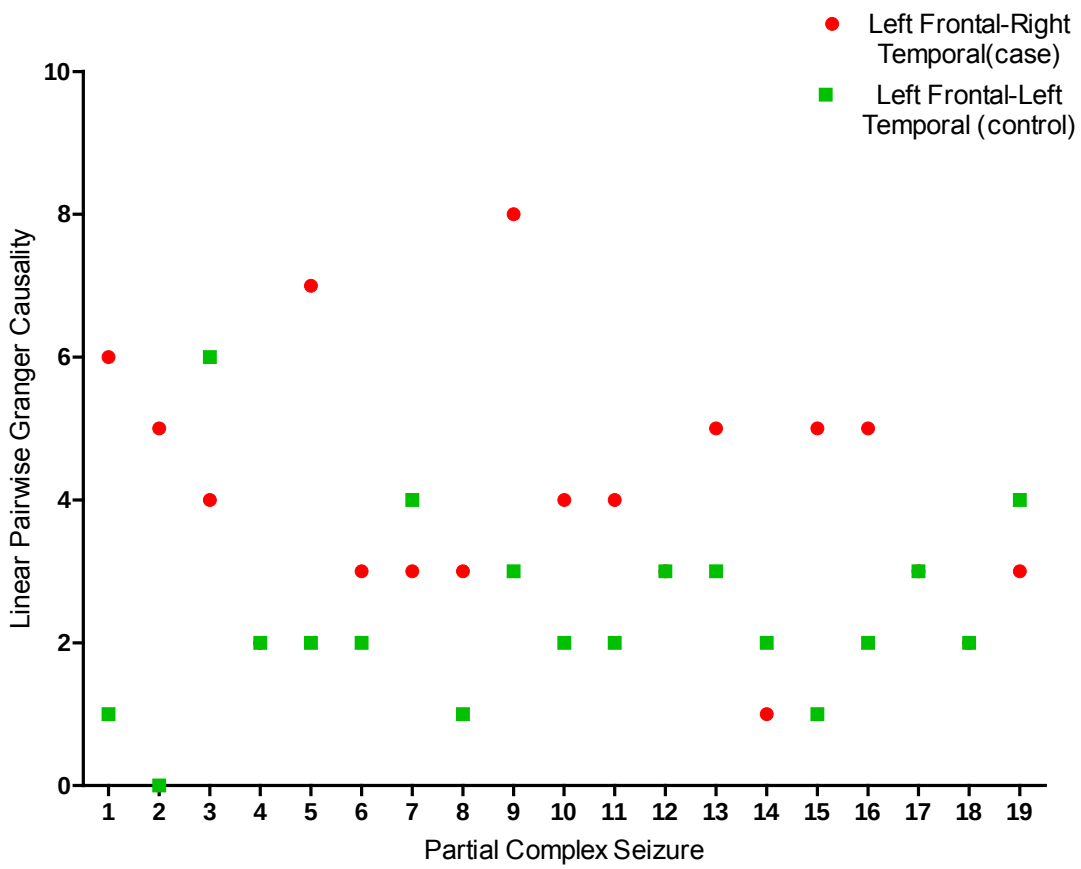

Figure 3-1. Seizure directionality of ictal events with onset over the left frontal lobe and demonstrating contra-lateral propagation (inter-hemispheric) as compared with controls.

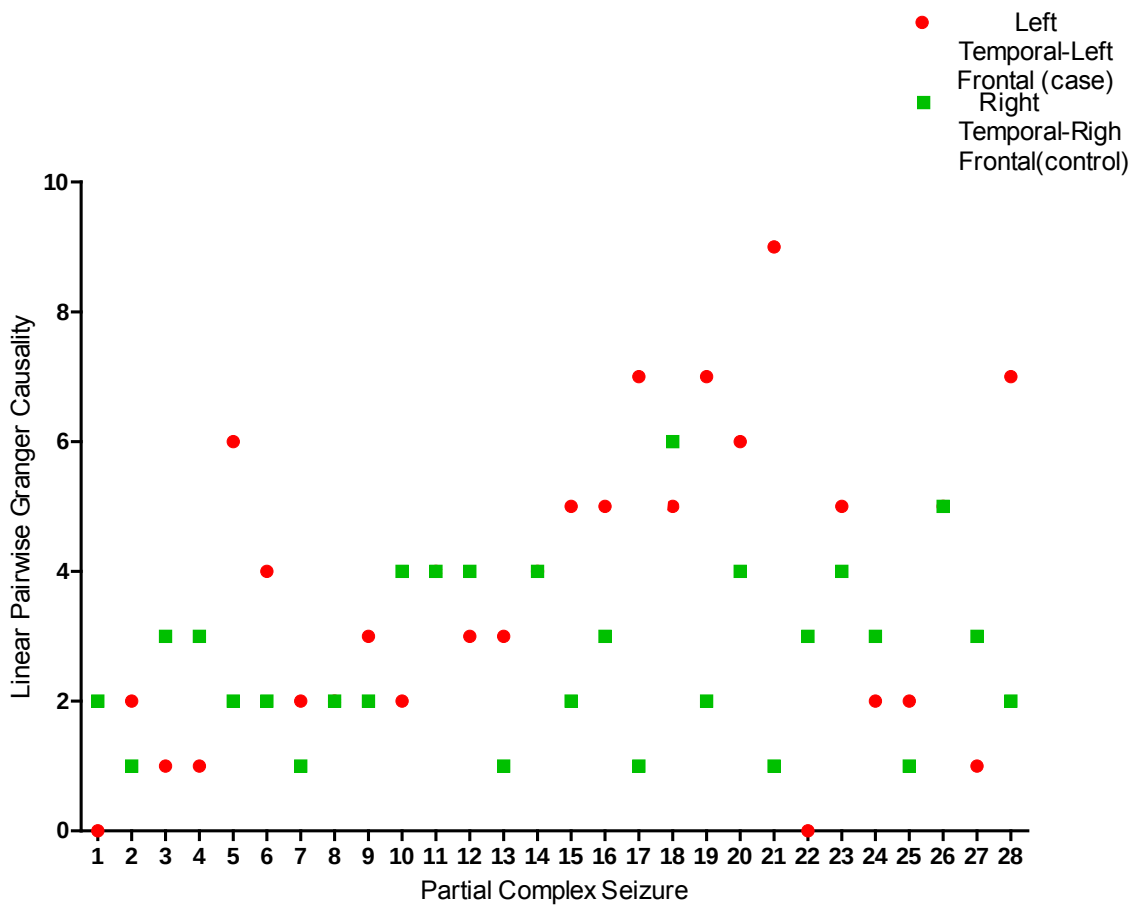

Figure 3-2. Scatter plot of linear PGC of events with an ictal onset over the left temporal lobe propagating ipsilaterally as compared against right temporal lobe controls.

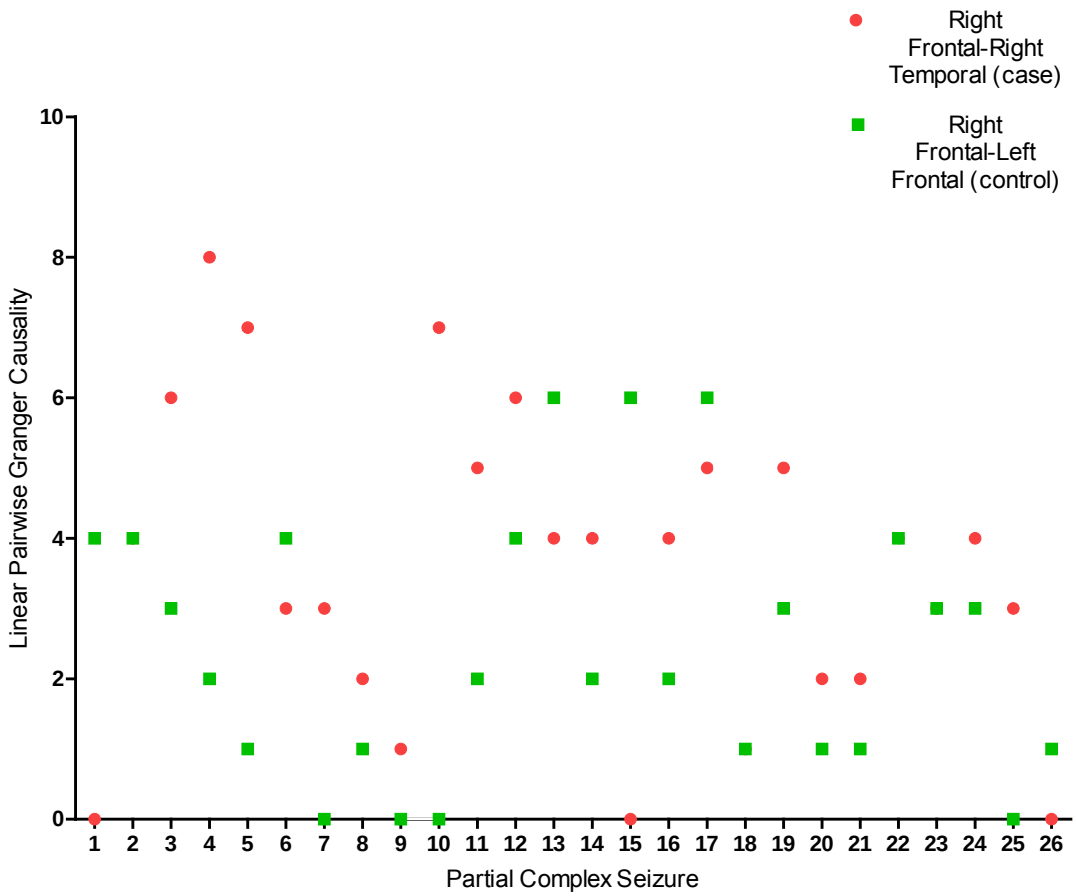

Figure 3-3. Intra-hemispheric directionality. Demonstrated here by the identification of a significant directionality within the right hemisphere (right frontal to right temporal) than across hemispheres (right frontal towards left frontal) using the same electrode (right frontal, F8) in both analysis.

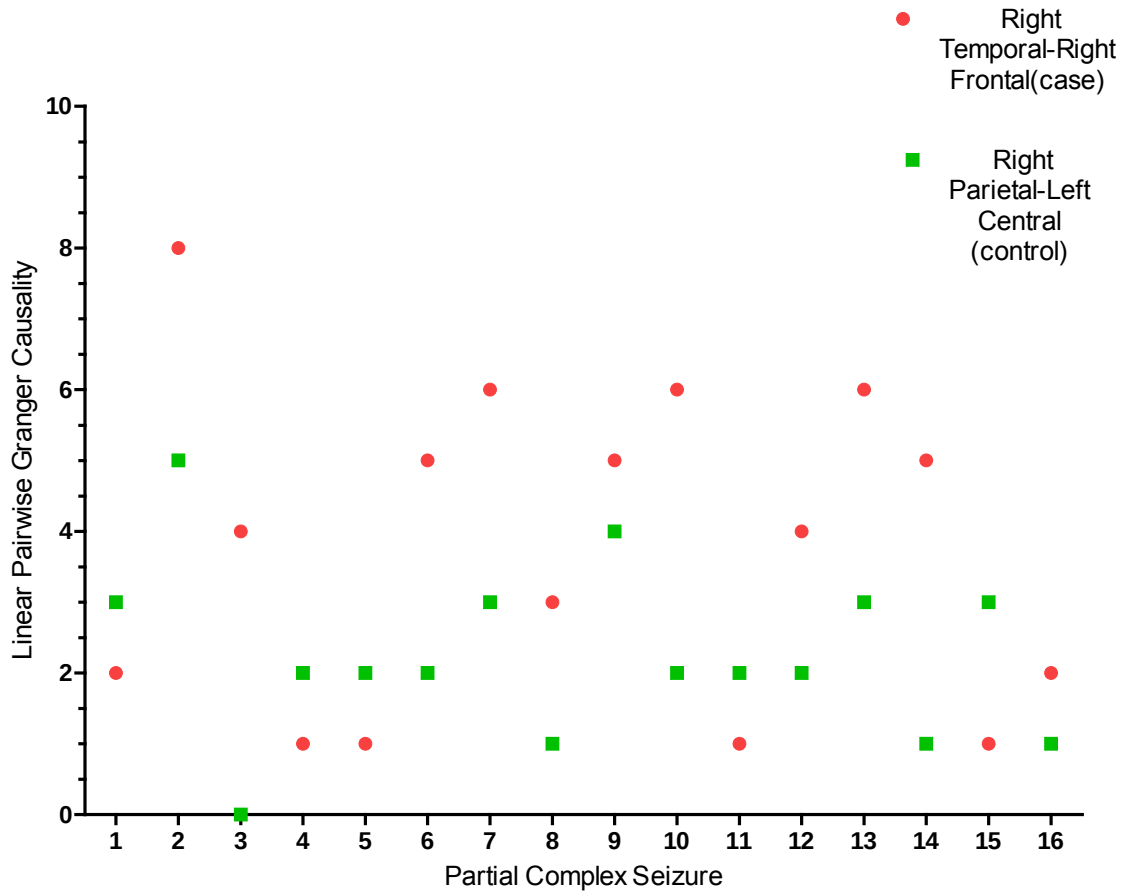

Figure 3-4. PGC in subjects with CPS with an ictal onset over the right temporal lobe network and using the right parietal network as a control demonstrating intra-hemispheric ictal spread.

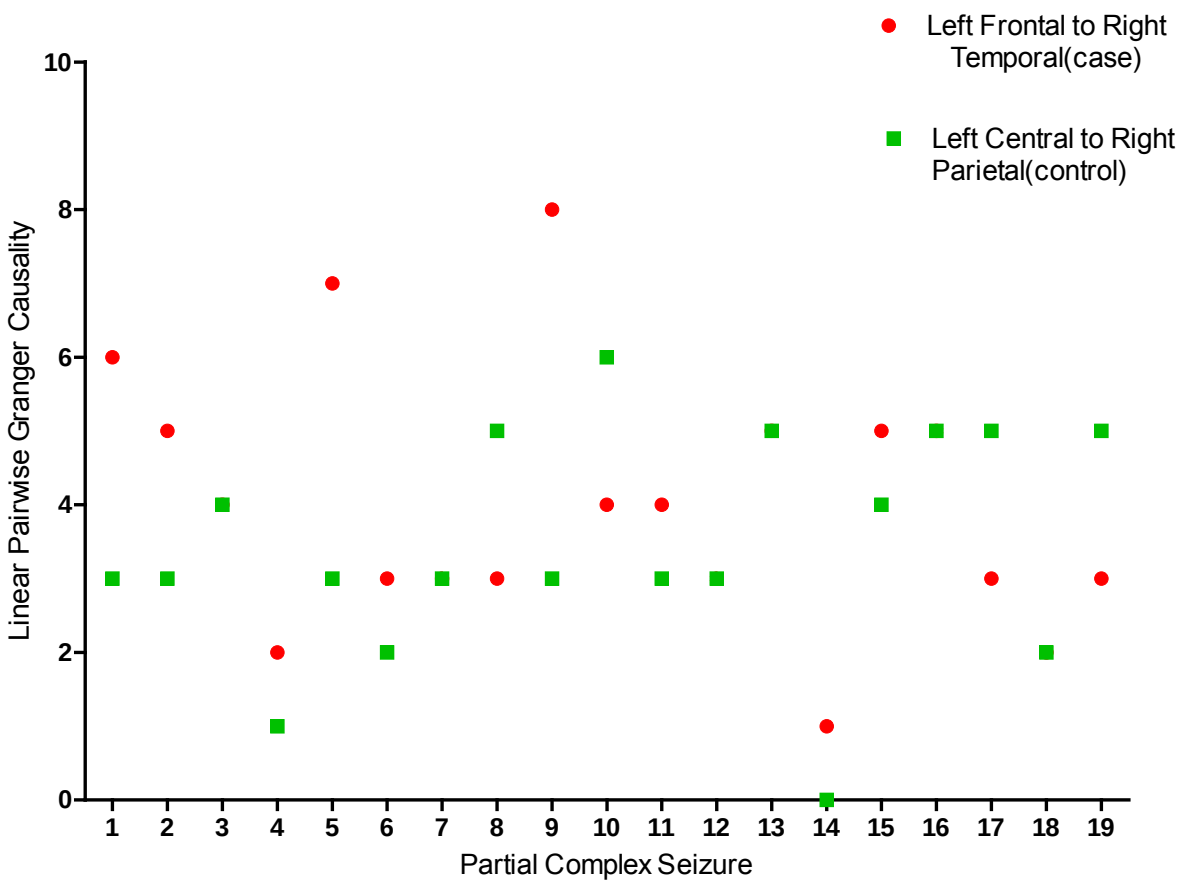

Figure 3-5. Seizure directionality of ictal events with onset over the left frontal network and compared against the left parietal network.

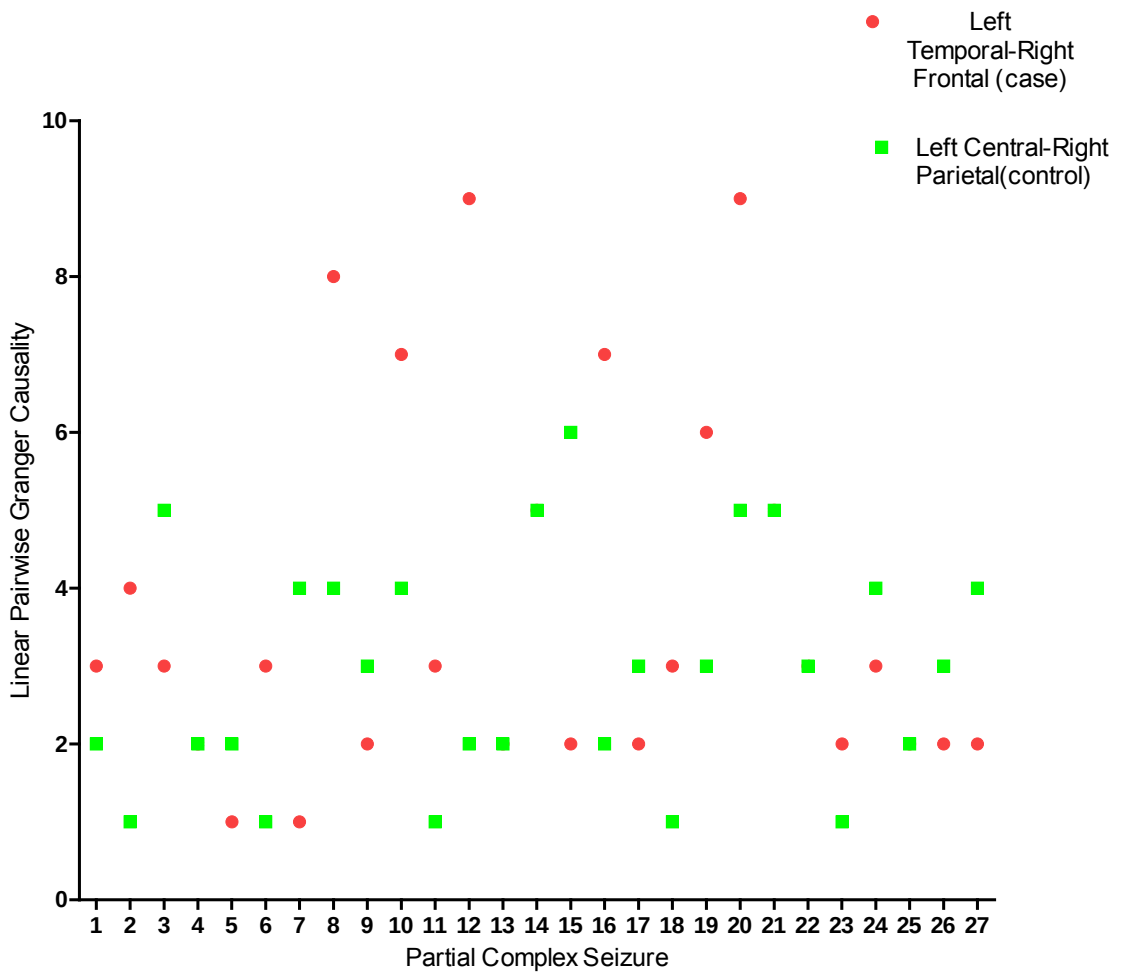

Figure 3-6. Seizure directionality of ictal events originating over the left temporal lobe and compared against the neighboring left parietal network.

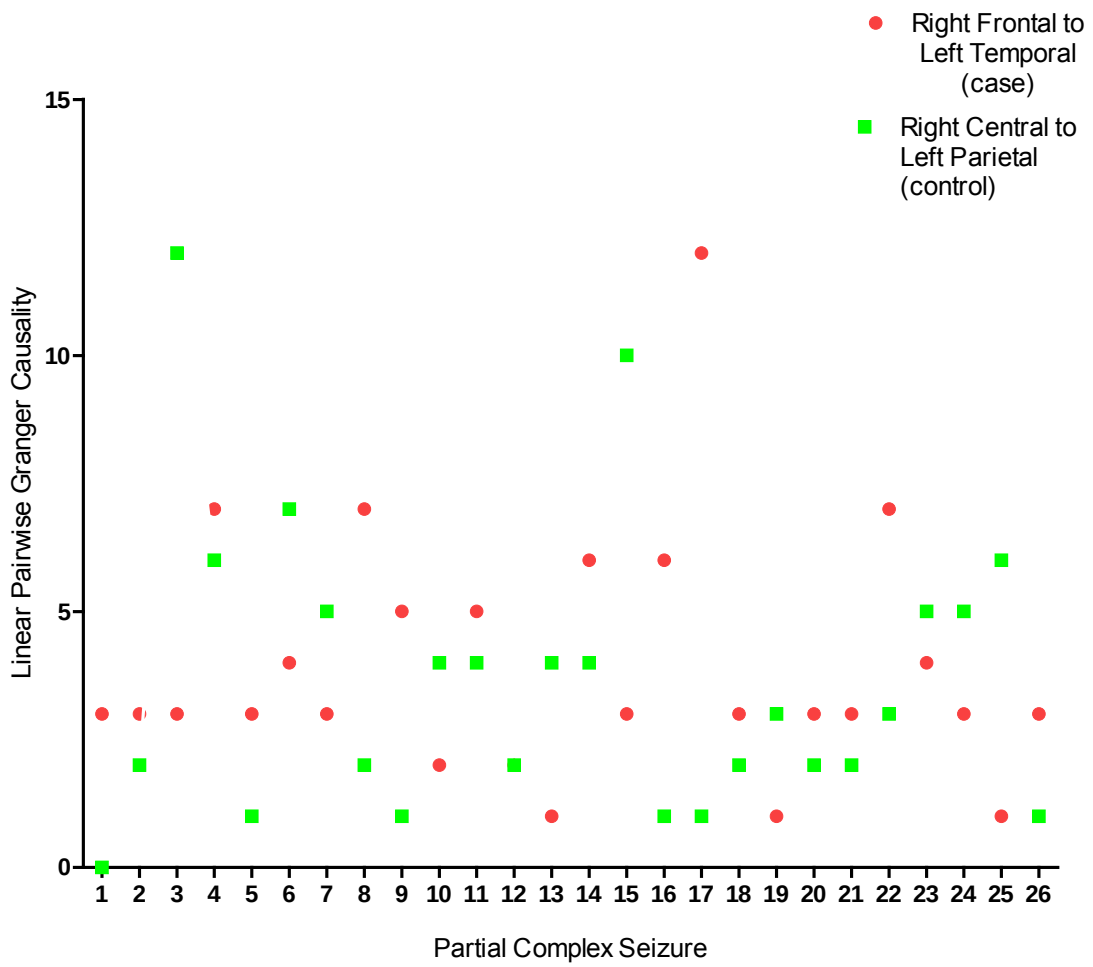

Figure 3-7. Seizure directionality of events with ictal onset over the right frontal region extending contra-laterally and compared against the right parietal network.

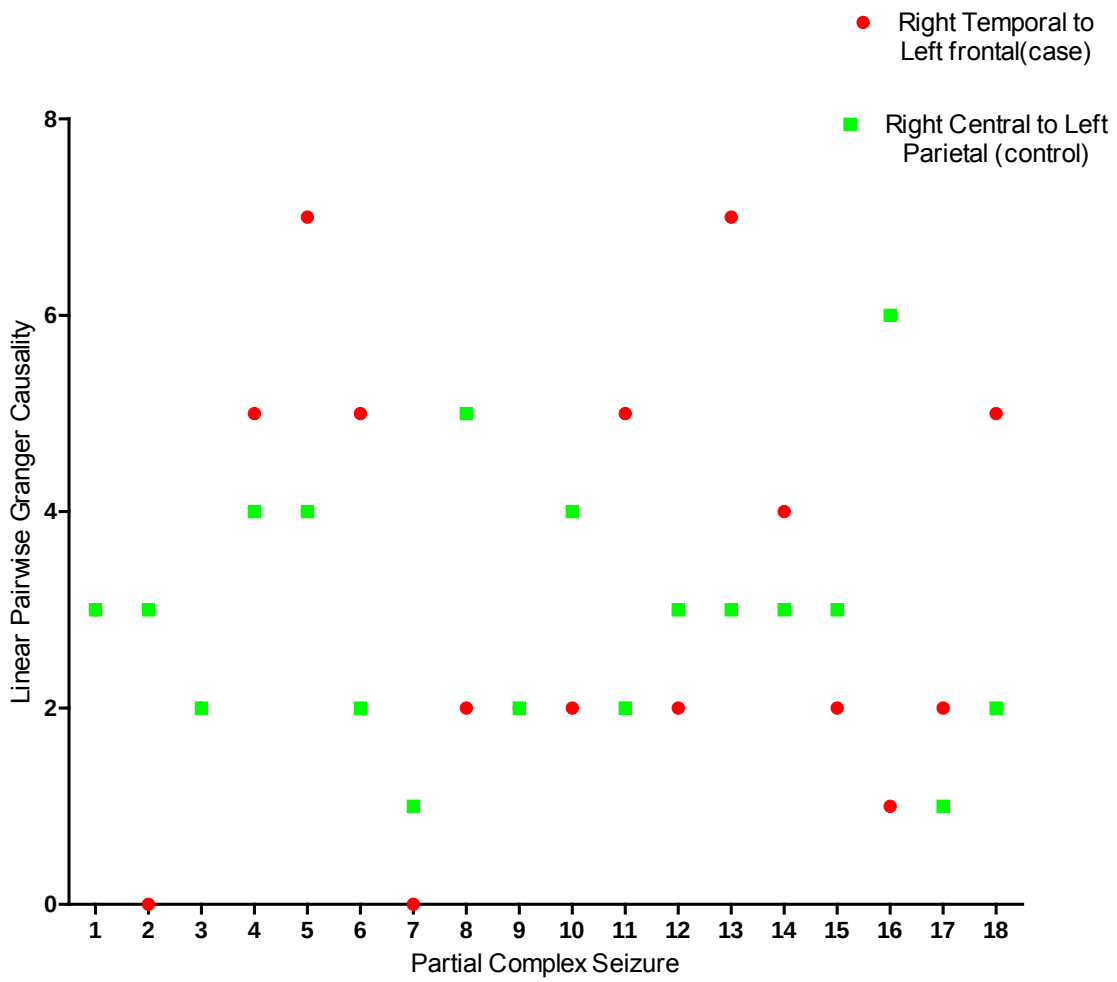

Figure 3-8. Seizure directionality to evaluate inter-hemispheric ictal spread on events with onset over the right temporal region extending towards the left frontal lobe and compared against right parietal networks controls.

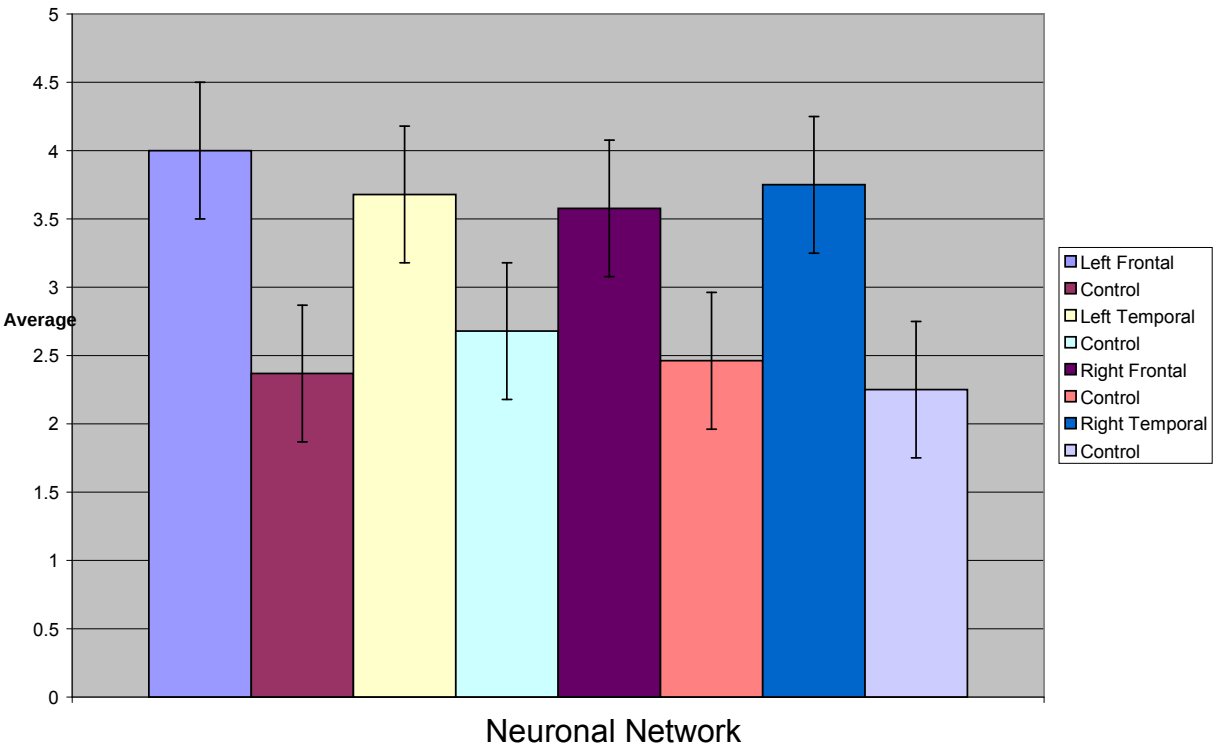

Figure 3-9. Average and standard deviation for seizure directionality over the mesio-limbic temporal network.

CHAPTER 4
DISCUSSION

One of the most important challenges facing the neurophysiologist in the study of epilepsy is to understand how structural network changes can lead to modifications in the function between unrelated or related brain networks. The work developed during this thesis project is driven by the overall hypothesis that such areas will correspond to the ictogenic networks identified in data sets using sophisticated connectivity measures and brain imaging techniques. Our findings demonstrated intra-hemispheric propagation using non-invasive scalp ictal recordings in subjects with seizures and IO over the MLTN. Such a finding may imply that no morphological or functional connectivity is established across hemispheres. However, prior studies have documented sequential directionalities between CA1 region and dentate gyrus within and across hippocampal formations using PGC.[11] Thus, it is possible that this non-invasive tool is not recording directional relationships within the complicated multi-neuronal network. Although our findings raise the provocative possibility that no inter-hemispheric ictal propagation occurs within unrelated neuronal networks as demonstrated by finding a non-significant p value for all inter-hemispheric measures tested within unrelated networks (left frontal p=0.2882, left temporal p=0.1572, right frontal p=0.6772, and, right temporal regions p= 0.7795), future studies may determine that one or more of the theories discussed in the introduction (e.g.“ the hidden unit” element), explains our findings.

Most striking was the fact that inter-hemispheric directionality was identified in the MLTN. Our interpretation of this finding is that directionality may be occurring within networks with similar phylogenic, embryological and functional characteristics such as the mesolimbic temporal networks. This is supported by the fact that no statistically

significant differences were identified when the MLTN was tested using PGC against the parietal network, ipsilaterally and contra-laterally. Overall, the detail information obtained of our PGC findings suggests the method is a useful tool to estimate onset and directionality between neuronal networks during seizure propagation. The significance of our finding may allow us to draw maps of functional connectivity in subjects with refractory seizures undergoing non-invasive presurgical evaluation. Accordingly, this non-invasive tool can be used in the analysis of scalp EEG ictal recordings and provide new information that empower the epileptologist to determine possible seizure onset. The functional maps obtained with PGC can be added to a well established wealth of tools available in clinical practice to better understand propagation when such conventional tools are not helpful. As a consequence, PGC analysis can help the clinical neurophysiologist to fine tune the determination ictal onset and apply such data in medical decision-making and during early stages of surgical planning.

In terms of defining a significant model order before computing PGC, a critical definition when analyzing raw EEG ictal data, our model was estimated using the multichannel BIC and the AIC criterion. This step not only allows for determination of the autoregressive model order but also provided verification that the data selected was suitable for analysis. The contrary was also true: failure to reach a minimum AIC/BIC did not permit selection of an appropriate model order and was indicative that the data are/were insufficient or inappropriate for Granger analysis. However, if no clear model was evident with AIC/BIC analysis, then such affected epochs were not used for analysis. Clearly, that affected our originally aimed sample size target.

Regarding the question of using the entire ictal EEG dataset or following a different approach such as data segmentation, we elected the former because two caveats: quasi-stationary segments are required and abrupt transition during sampling intervals must be avoided during segmentation. Preliminary review of the EEG data made us aware that was not possible to consistently avoid abrupt transition during sampling. Thus, we elected to follow a non-segmented methodology.

The known limitations of this study are following: 1) small sample population per each seizure group, 2) we did not look at the PGC changes in different frequency bands, and 3) we only analyzed the data of electrodes F7, F8, T7, T8, C3, C4, P7, and P8. Other electrodes could be added to the scalp EEG and/or more of the standard electrodes (Figure 2-1) could be included in the PGC assessment. However, the findings on this study support what is being identified using other methodologies in the animal model of limbic epilepsy: PGC may have a role in the evaluation of seizure propagation. The ultimate goal is to develop and validate, in both the animal model and human subjects, methods based on autoregressive analysis to provide insights into seizure localization when originating form temporal or extra-temporal regions (parietal networks, occipital networks, etc.), and when fast ictal activation precludes appropriate localization using visual analysis of the VEEG. Future methods should not utilize amplitude criteria but should allow appropriate detection of pre-ictal of fast activity as a method of prediction.

While visual analysis of the EEG recordings allows for a determination of a focal ictal onset in any of the four regions of interest studied, inspection of subsequent seizure recordings did not permit clear seizure localization once the activity has spread.

This study has demonstrated that analysis of PGC on human ictal epochs, allows statistical significant confirmation of the ictal directionality of clinical and electrographic seizures.

CHAPTER 5
CONCLUSIONS

The results of this study enhance our understanding of neuronal circuitry associated with epilepsy and will help interpreting current theories about ictogenesis and connectivity. Simultaneous video analysis and scalp EEG recordings from combined surface electrodes allowed for good confirmation of seizure onset in the fronto-temporal structures. Visual analysis of the scalp EEG recordings in patients with PCS with a suspected IO over the MTLN revealed a fairly common ictal pattern. Although the study is focused on prediction of directionality via PGC, the study findings also offer insights into other mechanisms underlying functional interactions in the normal and abnormal brain such as neuronal sprouting, traffic and regeneration after surgical resection. The information learned through this study will help us understanding other disorders of cortical cerebral dysfunction and co-registration with other indirect methods of neuronal activity such as MEG and functional MRI.

The data presented here provide the framework for the development of PGC based maps, enhances our knowledge of the epileptogenic networks and facilitate better identification of ictogenic areas not easily defined with conventional EEG. This information may prove useful in planning epilepsy surgery. Defining the precise margins of the IZ will minimize injury to healthy surrounding tissue when patients are referred for epilepsy surgery candidates. In addition, even a modest increase in the ability to better predict ictal onset would provide opportunities to improve long-term control. Ultimately, the development of new tools to identify mechanisms of directionality analysis and its strength using techniques such as effective and/or functional connectivity analysis, functional MRI, MEG, optical stimulation technologies, vector

transfection, and, together with clinical, functional and quality of life measurements will lead to new theories of ictogenic mechanisms and new strategies to improved approaches to seizure control in subjects with pharmaco-resistant epilepsy.

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BIOGRAPHICAL SKETCH

Edgard Andrade received his medical degree from the National University of Colombia where he graduated in the top 5% in his medical school class. He then completed training in pediatrics at the State University of New York-Woodhull Medical Center and successfully completed subspecialty training in child neurology at Vanderbilt University and in clinical neurophysiology at Miami Children's Hospital. He is board certified by the American Board of Pediatrics and the American Board of Neurology with special qualification in child neurology. He joined the College of Medicine at the University of Florida as an assistant professor in the Division of Pediatric Neurology in 2006. Dr. Andrade is a fellow of the American Academy of Pediatrics and member of the American Academy of Neurology, the Child Neurology Society, the Society for Neurosciences, the Spanish-American Association of Pediatric Neurology and the American Epilepsy Society. His research interest is in surgical epileptology and novel brain imaging technologies.